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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 495/04, A61K 31/505 // (C07D 495/04, 333:00, 239:00)

A1

(11) International Publication Number: WO 96/24597

(43) International Publication Date: 15 August 1996 (15.08.96)

(21) International Application Number: PCT/JP96/00263

(22) International Filing Date: 7 February 1996 (07.02.96)

(30) Priority Data:

7/20717	8 February 1995 (08.02.95)	JP
7/40151	28 February 1995 (28.02.95)	JP
PCT/JP95/00728	14 April 1995 (14.04.95)	WO
(34) Countries for which the regional or international application was filed:		US et al.
7/271638	19 October 1995 (19.10.95)	JP

(60) Parent Application or Grant
(63) Related by Continuation
US 08/454,304 (CIP)
Filed on 14 April 1995 (14.04.95)

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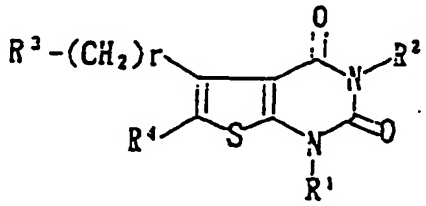
(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: THIENOPYRIMIDINE DERIVATIVES, THEIR PRODUCTION AND USE



(I)

(57) Abstract

A thienopyrimidine derivative of formula (I) is effective as a prophylactic or therapeutic agent for the prevention or treatment of several hormone dependent diseases, for example, a sex hormone dependent cancer (e.g. prostatic cancer, cancer of uterine cervix, breast cancer, pituitary adenoma), benign prostatic hypertrophy, myeloma of the uterus, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, polycystic ovary syndrome and acne vulgaris; is effective as a fertility controlling agent in both sexes (e.g. a pregnancy controlling agent and a menstrual cycle controlling agent); can be used as a contraceptive of male or female, as an ovulation-inducing agent of female; can be used as an infertility treating agent by using a rebound effect owing to a stoppage of administration thereof; is useful as modulating estrous cycles in animals in the field of animal husbandry, as an agent for improving the quality of edible meat or promoting the growth of animals; and is useful as an agent of spawning promotion in fish.

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DESCRIPTION

THIENOPYRIMIDINE DERIVATIVES, THEIR PRODUCTION AND USE

Technical Field

The present invention relates to novel thienopyrimidine derivatives and salts thereof. The present invention further relates to methods for manufacturing the thienopyrimidine derivatives and the salts thereof, and pharmaceutical compositions containing the thienopyrimidine derivatives.

Background Art

Secretion of anterior pituitary hormone is controlled by peripheral hormones secreted from target organs for the respective hormones and by secretion-accelerating or -inhibiting hormone from the hypothalamus, which is the upper central organ of the anterior lobe of the pituitary (in this specification, these hormones are collectively called "hypothalamic hormone"). At the present stage, as hypothalamic hormones, nine kinds of hormones including, for example, thyrotropin releasing hormone (TRH) or gonadotropin releasing hormone {GnRH: sometimes called LH-RH (luteinizing hormone releasing hormone)} have been confirmed (cf. Seirigaku 2, compiled by M. Iriku and K Toyama, published by Bunkohdo, p610-618, 1986). These hypothalamic hormones are assumed to show their actions via the receptor which is considered to exist in the anterior lobe of the pituitary (cf. ibid), and studies of receptor genes specific to these hormones, including those of humans, have been developed (Receptor Kiso To Rinshô, compiled by H. Imura, et al., published by Asakura Shoten, p297-304, 1993). Accordingly, antagonists or agonists specifically and selectively acting on these receptors control the

action of hypothalamic hormone and the secretion of anterior pituitary hormone. As a result, they are expected to be useful as prophylactic and therapeutic agents of anterior pituitary hormone dependent diseases.

Leuprorelin acetate (Fujino et al., Biological and Biophysical Research Communications, Vol.60, 00.406-413, 1974; Oliver, R.T.D. et al., British Journal of Cancers, Vol.59, p.823, 1989; and Toguchi et al., Journal of International Medical Research, Vol.18, pp.35-41), which is a highly potent derivative of gonadotropic hormone-releasing hormone, one of the hypothalamic hormones, (hereinafter sometimes abbreviated as GnRH) (Schally A. V. et at., Journal of Biological Chemistry, Vol. 246, pp.7230-7236, 1971; and Burgus, R. et al., Proceeding of Natural Academic Science, USA, Vol.69, pp278-282, 1972), by administration of multiple doses, lowers release of gonadotropic hormone in the pituitary, causing a lowering of reactivity of gonadotropic hormone in the sperm and ovary tissue to suppress secretion of testosterone and estrogen. Leuprorelin acetate has, therefore, been known to show antitumor activity on such hormone-dependent cancers as prostate cancer, and has been widely used in the clinical field. Leuprorelin acetate has been widely used clinically also as a therapeutic agent of e.g. endometriosis and precocious puberty. The high antitumor activity of leuprorelin acetate is assumed to be due to its high resistance, as compared with natural GnRH, against protease,and to its high affinity for GnRH receptor causing desensitization of GnRH due to decrease in number of receptors. However, as leuprorelin acetate is an ultra-agonist of GnRH receptors, it has been known that, immediately after the first administration, a transient aggravation accompanied with a rise of

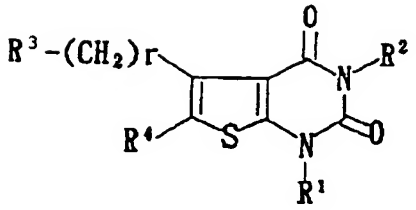
serum testosterone concentration due to pituitary-gonadotropic action (acute action) is observed. Under these circumstances, GnRH antagonistic drugs which are expected to have substantially the same therapeutic effects as described above but not to cause the above-mentioned transient pituitary-gonadotropic action (acute action) have been desired. As compounds having such GnRH antagonistic activity, a number of compounds including, for example, derivatives of GnRH such as straight-chain peptides, (US Patent No. 5140009 and No. 5171835), cyclic hexapeptide derivatives [Japanese Patent Application Laid-open No. 61(1986)-191698] or bicyclic peptide derivatives [Journal of medicinal chemistry, Vol.36, pp.3265-3273, 1993] have been disclosed. These compounds are, however, all peptides, which leave many problems including, for example, dosage forms, stability of drugs, durability of actions and stability on metabolism. For solving these problems, orally administrable GnRH antagonistic drugs, especially non-peptide ones, are strongly desired. At the present stage, however, no report on non-peptide GnRH antagonistic drugs has been made.

The object of the invention lies in providing novel compounds having excellent gonadotropic hormone releasing hormone antagonistic activity as well as excellent gonadotropic hormone releasing hormone antagonistic agents.

Disclosure of Invention

Thus, the present invention provides

(1). a novel thienopyrimidine derivative (I) of the formula:



(I)

wherein R^1 is hydrogen, an alkyl group or a group of the formula:

$$Q-(CH_2)p-$$

in which Q is (1) an aryl group which may be substituted by one or more of (i) halogen, (ii) nitro, (iii) cyano, (iv) amino, (v) an optionally substituted carboxyl, (vi) alkylenedioxy and (vii) a group of the formula: $-A-R^5$ in which A is a chemical bond or a spacer group and R^5 is an alkyl group, (2) an optionally substituted cycloalkyl group or (3) an optionally substituted heterocyclic group, and p is an integer of 0 to 3;

R^2 is hydrogen, an alkyl group which may be substituted by alkoxy, an optionally substituted aryl group, an optionally substituted aralkyl group or an optionally substituted cycloalkyl group;

R^3 is an optionally substituted amino group; r is an integer of 0 to 3; and

R^4 is an optionally substituted aryl group;

or a salt thereof;

(2). A compound according to the item (1), wherein the spacer group represented by A is -O- or -S(O)m- in which m is an integer of 0 to 2;

(3). A compound according to the item (1), wherein R^1 is a group of the formula:

$$Q-(CH_2)p-$$

in which Q is an aryl group which may be substituted by one or more of (i) halogen and (ii) a group of the formula: $-A-R^5$ in which A is -O- or -S(O)m- wherein m is an integer of 0 to 2 and R^5 is an alkyl group; and p

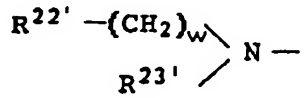
is an integer of 0 to 3;

(4). A compound according to the item (1), wherein R^2 is (1) an alkyl group which may be substituted by alkoxy, (2) an aryl group which may be substituted by one or more of (i) amino, (ii) acyl, (iii) carbamoyl, (iv) carboxy, (v) nitro, (vi) hydroxy, (vii) alkoxy group which may be substituted by alkoxy, (viii) halogen and (ix) a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is an alkyl group, (3) an aralkyl group which may be substituted by halogen or (4) a cycloalkyl group;

(5). A compound according to the item (4), wherein R^2 is (1) an alkyl group which may be substituted by alkoxy, (2) an aryl group which may be substituted by one or more of (i) hydroxy, (ii) alkoxy group which may be substituted by alkoxy, (iii) halogen and (iv) a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is an alkyl group, (3) an aralkyl group or (4) a cycloalkyl group;

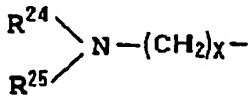
(6). A compound according to the item (4), wherein R^2 is an aryl group which may be substituted by one or more of (1) an alkoxy group which may be substituted by alkoxy, (2) halogen and (3) a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is an alkyl group;

(7). A compound according to the item (1), wherein R^3 is an optionally substituted amino group of the formula:



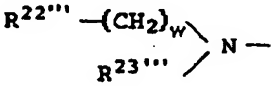
wherein $R^{22'}$ is (1) an aryl group which may be substituted by one or more of (i) amino, (ii) acyl, (iii) carbamoyl, (iv) carboxy, (v) nitro, (vi) hydroxy, (vii) alkoxy group which may be substituted by alkoxy, (viii) halogen, (ix) alkyl and (x) a group of the

formula: -S(O)n-R^6 in which n is an integer of 0 to 2 and R^6 is an alkyl group, (2) a heterocyclic group which may be substituted by one or more of (i) amino, (ii) acyl, (iii) carbamoyl, (iv) carboxy, (v) nitro, (vi) hydroxy, (vii) alkoxy group, (viii) halogen, (ix) alkyl and (x) a group of the formula: -S(O)n-R^6 in which n is an integer of 0 to 2 and R^6 is an alkyl group, (3) an aralkyl group which may be substituted by halogen, (4) a group of the formula:

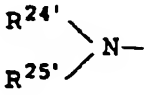


wherein R^{24} is hydrogen, an alkyl group or an aryl group, R^{25} is hydrogen or an alkyl group and R^{24} and R^{25} may form a 5 to 7 membered cyclic amino group containing the adjacent nitrogen atom which may be optionally substituted and x is an integer of 0 to 3 or (5) an alkyl group which may be substituted by alkylthio, w is an integer of 0 to 3; and $R^{23'}$ is hydrogen or an alkyl group;

(8). A compound according to the item (1), wherein R^3 is an optionally substituted amino group of the formula:



wherein $R^{22'''}$ is (1) an aryl group which may be substituted by alkylthio, (2) a heterocyclic group, (3) a group of the formula:

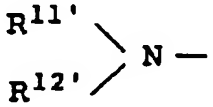


wherein $R^{24'}$ is hydrogen or alkyl, $R^{25'}$ is hydrogen or alkyl, and $R^{24'}$ and $R^{25'}$ may form a 5 to 7 membered cyclic amino group containing the adjacent nitrogen atom or (4) an alkyl group which may be substituted by

alkylthio, w is an integer of 0 to 3; and $R^{23'''}$ is hydrogen or an alkyl group;

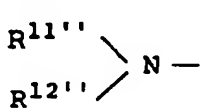
(9). A compound according to the item (1), wherein R^4 is an aryl group which may be substituted by one or more of (1) an optionally substituted amino group, (2) acyl, (3) an optionally substituted carbamoyl group, (4) carboxy, (5) nitro, (6) hydroxy, (7) an optionally substituted alkoxy group and (8) an optionally substituted alkenyl group;

(10). A compound according to the item (1), wherein R^4 is an aryl group which may be substituted by one or more of (1) a group of the formula:



wherein $R^{11'}$ is (i) hydrogen, (ii) alkyl, (iii) an optionally substituted alkoxy group, (iv) an optionally substituted acyl group or (v) a group of the formula: -S(O)n-R^6 in which n is an integer of 0 to 2, and R^6 is an alkyl group and $R^{12'}$ is hydrogen or alkyl, (2) acyl, (3) carbamoyl, (4) N-mono or di-alkylcarbamoyl, (5) nitro, (6) alkoxy which may be further substituted by one or more of alkoxy, alkanoyl, oxo, hydroxy, cycloalkyl and halogen, (7) alkenyl which may be further substituted by alkoxycarbonyl or alkylcarbonyl and (8) alkenyloxy;

(11). A compound according to the item (1), wherein R^4 is an aryl group which may be substituted by one or more of (1) a group of the formula:



wherein $R^{11''}$ is (i) hydrogen, (ii) alkyl, (iii) alkoxy which may be substituted by halogen or alkoxy, (iv) formyl, (v) alkanoyl which may be substituted by halogen or alkoxy, (vi) benzoyl or (vii) a group of the

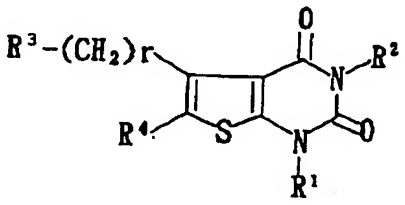
formula: -S(O)n-R^6 in which n is an integer of 0 to 2 and R^6 is an alkyl group and $R^{12''}$ is hydrogen or alkyl, (2) alkoxy which may be substituted by alkoxy, alkanoyl or cycloalkyl, (3) N-mono or di-alkylcarbamoyl, (4) nitro, (5) alkenyl which may be substituted by alkoxy-carbonyl or alkylcarbonyl or (6) alkenyloxy;

(12). A compound according to the item (1), which is 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-3-phenyl-1-(2-chloro-6-fluorobenzyl)-5-(N-benzyl-N-methylaminomethyl)thieno[2,3-d]pyrimidine or its salt;

(13). A compound according to the item (1), which is 2,4(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-6-(4-propionylaminophenyl)-5-(N-benzyl-N-methylaminomethyl)-3-(3-methoxyphenyl)thieno[2,3-d]pyrimidine or its salt;

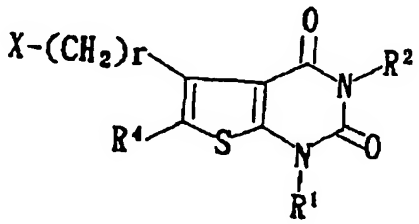
(14). A compound according to the item (1), which is 2,4(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-6-(4-isobutyrylaminophenyl)-5-(N-benzyl-N-methylaminomethyl)-3-(3-methoxyphenyl)thieno[2,3-d]pyrimidine or its salt;

(15). A method for producing a compound of the formula (I):



(I)

wherein R^1, R^2, R^3, R^4 and r have the same meaning as defined above or a salt thereof, which comprises reacting a compound of the formula:



(II)

wherein R^1, R^2, R^4 and r have the same meaning as defined above, X is a leaving group, or a salt thereof with compound of the formula:

$$R^3\text{-}H$$

wherein R^3 has the same meaning as defined above, or a salt thereof;

(16). A pharmaceutical composition, which comprises a compound as defined in the item (1) and a carrier, excipient or diluent therefor;

(17). A composition according to the item (16), which is a gonadotropin-releasing hormone antagonistic composition;

(18). A composition according to the item (16), which is a composition for preventing or treating a sex hormone dependent disease;

(19). A method for antagonizing gonadotropin-releasing hormone in a mammal, which comprises administering an effective amount of a compound as defined in the item (1) to a mammal suffering from a gonadotropin-releasing hormone derived disorder;

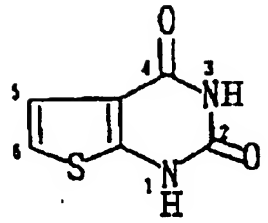
(20). A method according to the item (19), wherein the gonadotropin-releasing hormone derived disorder is a sex hormone dependent disease;

(21). A compound as defined in the item (1) for medicinal use;

(22). Use of a compound as defined in the item (1) for producing a gonadotropin-releasing hormone antagonistic composition for antagonizing gonadotropin-releasing hormone in a mammal suffering from a gonadotropin-releasing hormone derived disorder;

(23). Use according to the item (22), wherein the gonadotropin-releasing hormone derived disorder is a sex hormone dependent disease;

The nucleus of the present compound, 2,4(1H,3H)-dioxo- thieno[2,3-d]pyrimidine, is shown below;

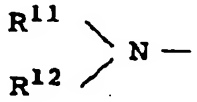


As the alkyl group shown by R^1, R^5 and alkyl which may be substituted by alkoxy shown by R^2, mention is made of, for example, C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, pentyl, hexyl). Among these, alkyl group having one to three carbon atoms is preferable.

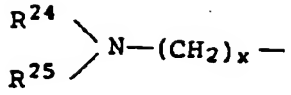
As the aryl group shown by Q or in the optionally substituted aryl group shown by R^2 and R^4, mention is made of, for example, mono cyclic- or condensed polycyclic-aromatic hydrocarbon residues. Preferable example of them includes C_{6-14} aryl such as phenyl, naphthyl, anthryl, phenanthryl, acenaphthylenyl and the like. Among these, phenyl, 1-naphthyl and 2-naphthyl are more preferable.

The number of substituents on the aryl group is one or more, preferably one to three. Examples of the substituents on the aryl group shown by R^2 and R^4 include (1) C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, pentyl, hexyl. The alkyl may be substituted by alkyl-carbonyl or alkoxy-carbonyl), (2) an optionally substituted alkenyl group such as C_{2-6} alkenyl (e.g. vinyl, allyl, 1-butenyl, 2-butenyl), which may be substituted by one or more of C_{1-10} acyl or C_{1-6} alkoxy-carbonyl, (3) C_{2-6} alkynyl (e.g. ethynyl, propargyl, 2-butynyl, 5-hexynyl), (4) C_{3-7} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), (5) C_{6-14} aryl (e.g. phenyl, naphthyl) which may be substituted by one or more of (i) halogen, (ii) alkyl, (iii) alkoxy which may be further substituted by alkoxy, (iv) nitro, (v) cyano, (vi) a

group $-S(O)_n-R^6$ wherein n is an integer of 0 to 2 and R^6 shows alkyl or amino, (vii) amino, (viii) acyl, (ix) carbamoyl, (x) carboxy and (xi) hydroxy, (6) heterocyclic group, for example, 5- to 9-membered aromatic heterocyclic group having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom (e.g. furyl, thienyl, pyrrolyl, thiazolyl, imidazolyl, pyrazolyl, pyridyl), or 5- to 9-membered nonaromatic heterocyclic group having 1 to 4 hetero atoms selected from a nitrogen atom, an oxygen atom and a sulfur atom (e.g. oxiranyl, azetidinyl, oxetanyl, thietanil, pyrrolidinyl, tetrahydrofuryl, thioranyl, piperidinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl), these heterocyclic group may be substituted by one or more of (i) halogen, (ii) alkyl, (iii) amino, (iv) acyl, (v) carbamoyl, (vi) carboxy, (vii) nitro, (viii) hydroxy, (ix) alkoxy and (x) a group of the formula: $-S(O)_n-R^6$ in which n is an integer of 0 to 2 and R^6 is alkyl group, (7) C_{7-13} aralkyl (e.g. benzyl, phenethyl, benzhydryl) which may be substituted by one or more of halogen, (8) an optionally substituted amino group such as a group of the formula:



wherein R^{11} denotes hydrogen; alkyl, e.g. C_{1-6} alkyl which may be substituted by hydroxy; acyl (e.g. C_{1-6} alkyl-carbonyl, formyl; arylcarbonyl) which may be substituted by one or more of halogen or alkoxy; optionally substituted alkoxy group as mentioned below; C_{3-7} cycloalkyl which may be substituted by one or more of hydroxy; a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is alkyl group and R^{12} denotes hydrogen or C_{1-6} alkyl, (9) a group of the formula:



wherein R^{24} is hydrogen, alkyl group or aryl group, R^{25} is hydrogen or alkyl group and R^{24} and R^{25} may form an optionally substituted 5 to 7 membered cyclic amino group containing the adjacent nitrogen atom and x is an integer of 0 to 3, (10) amidino, (11) acyl (e.g. C_{1-8} alkanoyl such as formyl, acetyl, propionyl, butyryl, octanoyl; C_{1-8} alkoxy-carbonyl such as methoxycarbony, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl; C_{6-14} aryl-carbonyl such as benzoyl; C_{8-11} aralkylcarbonyl such as benzylcarbonyl; C_{7-12} aralkyloxy-carbonyl such as benzyloxycarbonyl) which may be optionally substituted by one or more of substituents (e.g. halogen, alkylthio, alkoxy, oxo, hydroxy), (12) an optionally substituted carbamoyl group, e.g. carbamoyl, N-monosubstituted carbamoyl {e.g. N-(C_{1-7} alkyl)carbamoyl such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl}, N,N-disubstituted carbamoyl [e.g. N,N-di(C_{1-6} alkyl)carbamoyl such as dimethylcarbamoyl, diethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N-propyl-N-methylcarbamoyl}, (13) sulfamoyl, (14) N-monosubstituted sulfamoyl {e.g. N-(C_{1-6} alkyl)sulfamoyl such as methylsulfamoyl, ethylsulfamoyl, propylsulfamoyl}, (15) N,N-disubstituted sulfamoyl {e.g. N,N-di(C_{1-6} alkyl)sulfamoyl such as dimethylsulfamoyl, diethylsulfamoyl}, (16) carboxy, (17) C_{1-3} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl), (18) hydroxyl, (19) an optionally substituted alkoxy group, e.g. C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy, hexyloxy) which may have one or more of substituent (e.g. C_{1-6}

alkanoyl which is the same as above, C_{1-3} alkyl, halogen, C_{1-3} alkylthio, C_{1-3} alkoxy, oxo, hydroxy, C_{3-7} cycloalkyl which is the same as above), (20) C_{2-4} alkenyloxy (e.g. vinyloxy, allyloxy), (21) C_{3-7} cycloalkyloxy (e.g. cyclopropyloxy, cyclopentyloxy, cyclohexyloxy), (22) C_{7-13} aralkyloxy (e.g. benzyloxy, benzhydryloxy), (23) C_{6-14} aryloxy (e.g. phenyloxy, naphthyloxy), (24) mercapto, (25) C_{7-13} aralkylthio (e.g. benzylthio, benzhydrylthio), (26) C_{6-14} arylthio (e.g. phenylthio, naphthylthio), (27) a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is alkyl group (e.g. methylthio, ethylthio, propylthio, methylsulfinyl, ethylsulfinyl, propylsulfinyl, methylsulfonyl, ethylsulfonyl, propylsulfonyl), (28) C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, propylenedioxy), (29) sulfo, (30) cyano, (31) azide, (32) nitro, (33) nitroso, (34) halogen (e.g. fulorine, chlorine, bromine iodine), and the like.

As the cycloalkyl in the optionally substituted cycloalkyl shown by Q of R^1 and R^2, mention is made of, for example, C_{3-10} cycloalkyl and C_{3-10} bicycloalkyl. The preferable examples of them include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2,2,1]heptyl, bicyclo[2,2,2]octyl, bicyclo[3,2,1]octyl, bicyclo[3,2,1]nonyl, bicyclo[4,2,1]nonyl, bicyclo[4,3,1]decyl. Among these, cyclopentyl and cyclohexyl are more preferable. The substituents are of the same meaning as definede in the substituents which aryl, shown by R^2 and R^4, may have. Preferred examples of the substituents are alkyl, alkoxy or halogen.

As the heterocyclic group in the optionally substituted heterocyclic group shown by Q of R^1, mention is made of, for example, 5- to 13-membered

aromatic heterocyclic group having one to four hetero atom(s) selected from an oxygen atom, a sulfur atom and a nitrogen atom; or saturated or unsaturated non-aromatic heterocyclic group.

Examples of the aromatic heterocyclic group include an aromatic monocyclic heterocyclic group (e.g. furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl), an aromatic condensed-ring heterocyclic group {e.g. benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzoimidazolyl, benzoxazolyl, 1,2-benzoisoxazolyl, benzothiazolyl, 1,2-binzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthylidinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyridazinyl, 1,2-4-tiazolo[4,3-a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl}. Examples of the non-aromatic heterocyclic group include oxylanyl, azetizinyl, oxethanyl, thiethanyl, pyrrolidinyl, tetrahydrofuranyl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl. Among these, furyl, thienyl, thiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, benzofuryl, indolyl and quinolyl are preferable.

The heterocyclic group may have one or more substituents, preferably one to three substituents. The substituents are of the same meaning as defined in the optionally substituted aryl shown by R^2 and R^4. Preferred examples of the substituents are halogen, alkyl, alkylthio or alkoxy.

As the halogen, as the substituent of the aryl shown by Q, mention is made of fluorine, chlorine, bromine, iodine.

As the substituents of the optionally substituted carboxyl of the aryl group shown by Q, mention is made of alkyl, cycloalkyl, aryl, aralkyl and heterocyclic group which are of the same meaning as defined above and below.

As the lower alkylenedioxy as the substituent of aryl group shown by Q, mention is made of, for example, C_{1-6} alkylenedioxy. Examples of the alkylenedioxy includes methylenedioxy, ethylenedioxy, propylenedioxy, 2,2-dimethylmetylenedioxy.

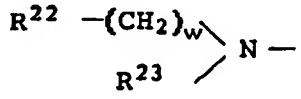
As the spacer group shown by the symbol "A", mention is made of, for example, C_{1-4} alkylene (e.g. methylene, ethylene), C_{2-6} alkenylene (e.g. vinylene, butadienylene); a group of the formula: $-(CH_2)cNR^{26}-$ in which c is 0 to 3, R^{26} is hydrogen, C_{1-6} alkyl (e.g. methyl, ethyl, butyl); a group of the formula: -CO-; a group of the formula: $-CONR^{27}-$ in which R^{27} is hydrogen, C_{1-6} alkyl (Examples of the alkyl are made of those mentioned above), C_{3-7} cycloalkyl (Examples of the cycloalkyl are made of those mentioned above), C_{6-14} aryl (Examples of the aryl are made of those mentioned above), a heterocyclic group (Examples of the heterocyclic group are made of those mentioned above); a group of the formula: $-S(O)_m-$ wherein m is an integer of 0 to 2; -O-; a group of the formula; $-NR^{27}S(O)_z-$ wherein z is an integer of 0 to 2,

R^{27} is of the same meaning as defined in the above.

As the alkoxy which may be the substituent of the alkyl group shown by R^2, mention is made of C_{1-6} alkoxy.

As the aralkyl in the optionally substituted aralkyl shown by R^2, mention is made of, for example, aryl-alkyl. The aryl is of the same meaning as defined above. Examples of the alkyl include C_{1-6} alkyl such as methyl, ethyl, propyl, butyl, pentyl, hexyl. The substituents on the aralkyl shown by R^2 are of the same meaning as defined in the substituents which aryl group shown by R^2 and R^4 may have.

As the optionally substituted amino group shown by R^3, mention is made of, for example, (1) a group of the formula:



wherein R^{22} is an alkyl, cycloalkyl, aryl or heterocyclic group and these groups may optionally be substituted,w is an integer of 0 to 3, R^{23} is hydrogen or an optionally substituted alkyl, or (2) hexamethylenetetraamino. The substituents on the alkyl, cycloalkyl, aryl and heterocyclic groups in the above R^{22} and R^{23} are of the same meaning as defined in the substitution on ary group shown by R^2 and R^4 as mentioned above.

As the preferable spacer group represented by A in the definition of the substituents on the aryl group of Q in R^1, mention is made of -O- or -S(O)m- in which m is an integer of 0 to 2.

As preferred examples of the above group R^1, mention is made of the group of the formula: Q-(CH_2)p- wherein Q and p has the same meaning as defined above.

As preferred examples of the above group R^1, mention is made of hydrogen or a group of the

formula: $-(CH_2)_pQ'$ wherein Q' denotes an aryl group which may be substituted by halogen, nitro, cyano, amino or a group of the formula: $-A'-R^{5'}$ (wherein A' denotes -O- or -S- and $R^{5'}$ denotes alkyl), and p has the same meaning as defined above.

As more preferred examples of the above group R^1, mention is made of a group of the formula:

$$Q-(CH_2)p-$$

in which Q is an aryl group which may be substituted by one or more of (i) halogen and (ii) a group of the formula: $-A-R^5$ in which A is -O- or -S(O)m- in which m is an integer of 0 to 2 and R^5 is alkyl group; and p is an integer of 0 to 3.

As still more preferable examples of the group R^1, mention is made of C_{6-14} aryl-methyl which may be substituted by halogen or a group $-A''-R^{5''}$ wherein A" is -O- or -S- and $R^{5''}$ is alkyl.

As especially preferable example of the group R^1, mention is made of the group $Q'''-(CH_2)p-$ wherein Q''' is an aryl group which may be substituted by halogen and p is an integer of 0 to 3.

As preferred examples of the group R^2, mention is made of (1) an alkyl group which may be substituted by alkoxy, (2) an aryl group which may be substituted by one or more of (i) amino, (ii) acyl, (iii) carbamoyl, (iv) carboxy, (v) nitro, (vi) hydroxy, (vii) alkoxy group which may be substituted by alkoxy, (viii) halogen and (iv) a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is alkyl group, (3) an aralkyl group which may be substituted by halogen or (4) cycloalkyl group.

As more preferred examples of the group R^2, mention is made of (1) C_{1-6} alkyl which may be substituted by C_{1-3} alkoxy, (2) C_{6-14} aryl which may be substituted by one or more of amino, acyl, carbomoyl,

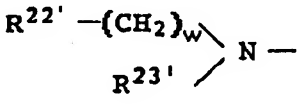
carboxyl, nitro, hydroxy, C_{1-3} alkoxy, sulfo, halogen and a group of the formula: $-S(O)_n-R^6$ wherein n is an integer of 0 to 2 and R^6 is C_{1-3} alkyl, or (3) C_{3-10} cycloalkyl.

As further more preferred examples of the group R^2, mention is made of (1) an alkyl group which may be substituted by alkoxy, (2) an aryl group which may be substituted by one or more of (i) hydroxy, (ii) alkoxy group which may be substituted by alkoxy, (iii) halogen and (iv) a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is an alkyl group, (3) aralkyl group or (4) a cycloalkyl group.

As more preferable examples of the group R^2, mention is made of (1) C_{1-6} alkyl which may be substituted by C_{1-3} alkoxy, (2) C_{6-14} aryl which may be substituted by one or more of C_{1-3} alkoxy and a group of the formula: $-S(O)n-R^6$ wherein n is an integer of 0 to 2 and R^6 is C_{1-3} alkyl, or (3) C_{3-10} cycloalkyl.

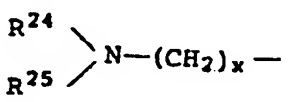
As the most preferred examples of the group R^2, mention is made of the aryl group which may be substituted by one or more of (1) an alkoxy group which may be substituted by alkoxy, (2) halogen and (3) a group of the formula: $-S(O)n-R^5$ in which n is an integer of 0 to 2 and R^5 is an alkyl group.

As preferred examples of the above group R^3, mention is made of hexamethylenetetraamino or a substituted amino group of the formula:



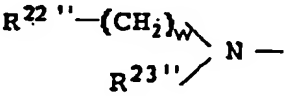
wherein $R^{22'}$ is (1) an aryl group which may be substituted by one or more of (i) amino, (ii) acyl, (iii) carbamoyl, (iv) carboxy, (v) nitro, (vi) hydroxy, (vii) alkoxy group which may be substituted by alkoxy, (viii) halogen, (ix) alkyl or (x) a group of the

formula: -S(O)n-R^6 in which n is an integer of 0 to 2 and R^6 is alkyl group, (2) heterocyclic group which may be substituted by one or more of (i) amino, (ii) acyl, (iii) carbamoyl, (iv) carboxy, (v) nitro, (vi) hydroxy, (vii) alkoxy, (viii) halogen, (ix) alkyl or (x) a group of the formula: -S(O)n-R^6 in which n is an integer of 0 to 2 and R^6 is alkyl group, (3) an aralkyl group which may be substituted by halogen, (4) a group of the formula:



wherein R^{24} is hydrogen, an alkyl group or an aryl group, R^{25} is hydrogen or an alkyl group and R^{24} and R^{25} may form an optionally substituted 5 to 7 membered cyclic amino group containing the adjacent nitrogen atom and x is an integer of 0 to 3 or (5) an alkyl group which may be substituted by alkylthio, w is an integer of 0 to 3; and $R^{23'}$ is hydrogen or an alkyl group.

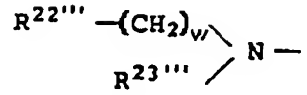
As more preferred examples of the above group R^3, mention is made of hexamethylenetetraamino or a group of the formula



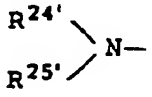
(wherein $R^{22''}$ denotes (1) alkyl, (2) phenyl which may be substituted by one or more of halogen, nitro, alkyl and a group of the formula: -$S(O)_n$-R^6 wherein n is an integer of 0 to 2 and R^6 is an alkyl group or an amino group, (3) a heterocyclic group which may be substituted by one or more of halogen and alkyl or (4) N-alkylcarbamoyl, w is an integer of 0 to 3; $R^{23''}$ denotes hydrogen or alkyl).

As more preferred examples of the above R^3,

mention is made of a substituted amino group of the formula:

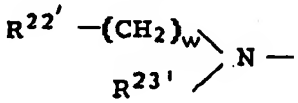


wherein $R^{22'''}$ is (1) aryl group which may be substituted by alkylthio, (2) heterocyclic group, (3) a group of the formula:



wherein $R^{24'}$ is hydrogen or alkyl and $R^{25'}$ is hydrogen or alkyl and $R^{24'}$ and $R^{25'}$ may form a 5 to 7 membered cyclic amino group containing the adjacent nitrogen atom or (4) an alkyl group which may be substituted by alkylthio, w is an integer of 0 to 3; and $R^{23'''}$ is hydrogen or an alkyl group.

As preferred examples of the above group R^3, mention is made of a group of the formula:

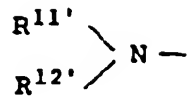


(wherein $R^{22'}$ is phenyl or pyridyl, these groups being unsubstituted or substituted by a group of the formula: $-S(O)_n-R^6$ in which n is an integer of 0 to 2 and R^6 is an alkyl group, w is an integer of 0 to 3. $R^{23'}$ is hydrogen or an alkyl group).

As preferred examples of the group R^4, mention is made of the aryl group which may be substituted by one or more of (1) an optionally substituted amino group, (2) acyl, (3) an optionally substituted carbamoyl group, (4) carboxy, (5) nitro, (6) hydroxy, (7) an optionally substituted alkoxy group and (8) an optionally substituted alkenyl group.

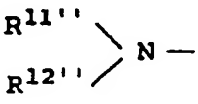
As more preferred examples of the above group R^4, mention is made of the aryl group which may be substituted by one or more of (1) a group of the

formula:



wherein $R^{11'}$ is (i) hydrogen, (ii) alkyl, (iii) an optionally substituted alkoxy group, (iv) an optionally substituted acyl group or (v) a group of the formula: -S(O)n-R^6 in which n is an integer of 0 to 2 and R^6 is an alkyl group and $R^{12'}$ is hydrogen or an alkyl group, (2) acyl, (3) carbamoyl, (4) N-mono or di-alkylcarbamoyl, (5) nitro, (6) alkoxy which may be substituted by one or more of alkoxy, alkanoyl, oxo, hydroxy, cycloalkyl and halogen, (7) alkenyl which may be substituted by alkoxycarbonyl or alkylcarbonyl and (8) alkenyloxy.

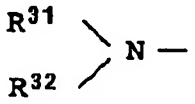
Further preferred examples of the above group R^4, mention is made of the aryl group which may be substituted by one or more of (1) a group of the formula:



wherein $R^{11''}$ is (i) hydrogen, (ii) alkyl, (iii) alkoxy which may be substituted by halogen or alkoxy, (iv) formyl, (v) alkanoyl which may be substituted by helogen or alkoxy, (vi) benzoyl or (vii) a group of the formula: -S(O)n-R^6 in which n is an integer of 0 to 2 and R^6 is an alkyl group and $R^{12''}$ is hydrogen or alkyl, (2) alkoxy which may be substituted by alkoxy, alkanoyl or cycloalkyl, (3) N-mono or di-alkylcarbamoyl, (4) nitro, (5) alkenyl which may be substituted by alkoxycarbonyl or alkylcarbonyl or (6) alkenyloxy.

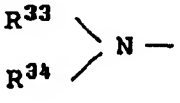
Further preferred examples of the aryl group in the above optionally substituted aryl R^4, mention is made of phenyl. As the preferred examples of the

substituents on the aryl group shown by R^4, mention is made of amino, acyl, carbamoyl, N-monosubstituted alkylcarbamoyl, carboxyl, nitro, hydroxy, C_{1-3} alkoxy which may be substituted by C_{1-3} alkoxy, a group of the formula:



(wherein R^{31} denotes C_{1-6} alkyl; C_{1-3} alkoxy which may be substituted by C_{1-3} alkoxy; or formyl, R^{32} denotes hydrogen or C_{1-6} alkyl), or C_{2-4} alkenyl which may be substituted by alkoxy-carbonyl or alkyl-carbonyl.

As a more preferred example of aryl in the optionally substituted aryl of the group R^4, mention is made of phenyl. As more preferred examples of the substituents on the aryl group shown by R^4, mention is made of amino; acyl; N-substituted alkylcarbamoyl; nitro; C_{1-3} alkoxy which may be substituted by C_{1-3} alkoxy; a group of the formula;



(wherein R^{33} denotes C_{1-6} alkyl, C_{1-3} acyl which may be substituted by C_{1-3} alkoxy; C_{1-3} alkoxy which may be substituted by C_{1-4} acyl; benzoyl; or formyl, R^{34} denotes hydrogen or C_{1-6} alkyl), C_{2-4} alkenyl which may be substituted by C_{1-3} alkoxy-carbonyl or C_{1-3} alkyl-carbonyl.

In the above each groups, the number of the substituents is preferably 1 to 3. r is preferably 1, p is preferably 1, and w is preferably 1.

As the 5 to 7 membered cyclic amino group containing nitrogen atom, mention is made of pyrrolidinyl, pyrrolinyl, pyrrolyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, imidazolidinyl, imidazolinyl,

imidazolyl, 1,2,3-triazinyl, 1,2,3-triazolidinyl, 1,2,3-triazolyl, 1,2,3,4-tetrazolyl, piperidinyl, piperazinyl, hexamethyleneamino, oxazolidino, morpholino, thiazolidino or thiomorpholino. As more preferable cyclic amino group, mention is made of pyrolidinyl, pyrazolinyl, pyrazolyl, piperidinyl, piperazinyl, morpholino and thiomorpholino.

The cyclic amino group may be substituted. The examples of the substituents includes C_{1-6} alkyl, C_{6-14} aryl, C_{7-10} aralkyl, benzhydryl, C_{1-6} alkyl-carbonyl, C_{6-14} aryl-carbonyl, C_{1-6} alkoxy-carbonyl. As the preferable substituent, mention is made of C_{1-6} alkyl, preferably C_{1-3} alkyl.

As the preferable alkyl in the above definition, mention is made of, for example, C_{1-10} alkyl. Examples of the alkyl includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl and hexyl. Among these, alkyl having one to six carbon atoms is more preferable, and alkyl having one to three carton atoms in still preferable.

As the acyl, mention is made of C_{1-10} acyl and the examples of the acyl are for example alkanoyl, aryl-carbonyl, aralkyl-carbonyl and aralkyloxy-carbonyl which are mentioned above.

As the preferable acyl and alkanoyl in the above definition, mention is made of alkyl-carbonyl, and alkyl is of the same meaning as defined above.

As the preferable alkoxy in the above adefinition, mention is made of C_{1-6} alkoxy, and examples of the alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy. Among these, alkoxy having 1 to 3 carbon atoms is preferable.

As the preferable alkenyl in the above definition, mention is made of C_{2-4} alkenyl. Examples of the alkenyl includes vinyl, allyl, 1-butenyl, 2-butenyl.

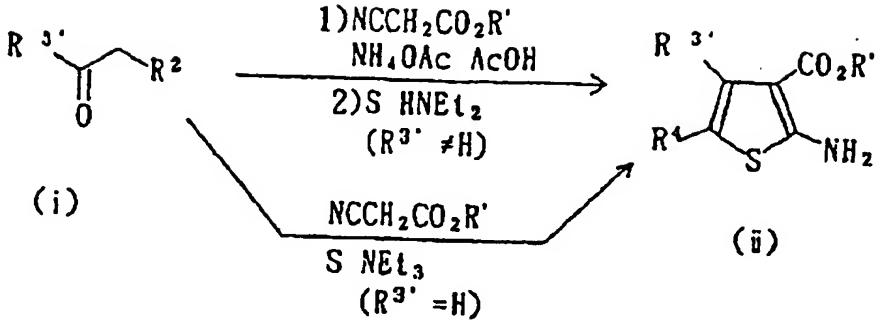
As the preferable aryl in the above definition, mention is made of C_{6-14} aryl. Examples of the aryl includes phenyl, naphthyl.

As the preferable aralkyl in the above definition, mention is made of C_{7-10} aralkyl. Examples of the aralkyl includes benzyl, phenethyl.

As the halogen, mention is made of fluorine, chlorine, bromine, iodine.

The compounds (I) of the present invention can be produced easily by per se known methods, as exemplified by the following production methods, or a similar method thereto.

1. Method A: In accordance with the method disclosed by K. Gewald, E. Schinke and H. Bøttcher, Chem. Ber., 99, 94-100 (1966), an adequate ketone or aldehyde having an active methylene (i) is allowed to react with a cyanoacetic acid ester derivative and sulfur to convert into a 2-aminothiophene derivative (ii). More specifically, in the case of using ketone ($R^{3'} \neq H$), it is subjected to heating under reflux together with a cyanoacetic acid ester derivative, in the presence of acetic acid and ammonium acetate, in a proper solvent such as toluene to give an alkylidene cyanoacetic acid ester derivative, which is then heated in an adequate solvent, for example, ethanol in the presence of sulfur and a base to afford a 2-aminothiophene derivative (ii). And, in the case of using aldehyde ($R^{3'}=H$), it is heated in a proper solvent, for example, dimethylformamide, in the presence of a cyanoacetic acid ester derivative, sulfur and a base to give a 2-aminothiophene derivative (ii).



The 2-aminothiophene derivative (ii) produced by the method described in Production Method 1 or a salt thereof is allowed to react with an isocyanate derivative. The isocyanate derivative is exemplified by derivatives represented by the formula, R^2-NCO (wherein R^2 is of the same meaning as defined above). The reaction of the compound (ii) or a salt thereof with the isocyanate derivative is conducted in an solvent which does not adversely affect the reaction (e.g. tetrahydrofuran, pyridine, dioxane, benzene, dichloromethane, 1,2-dichloroethane, toluene, xylene) at temperatures ranging from about 15 to about 130°C. The isocyanate derivative is employed in an amount of about 1 to 5 equivalents, preferably about 1.1 to 2.5 equivalents, relative to 1 equivalent of the compound (ii). The reaction time ranges from several hours to several days, preferably from about 15 minutes to about two days.

2. Method B: Amine [e.g. a compound represented by the formula R^2-NH_2 (wherein R^2 is of the same meaning as defined above)] is subjected to addition reaction to an isocyanate derivative produced by allowing a 2-aminothiophene derivative (ii) or a salt thereof to react with phosgene or an equivalent compound thereof [e.g. diphosgene such as bis(trichloromethyl)carbonate, triphosgene such as trichloromethylchloroformate]. The reaction of the compound (ii) or a salt thereof with phosgene or an equivalent compound thereof is conducted

in a solvent which does not affect adversely the reaction (e.g. dioxane, tetrahydrofuran, benzene, toluene, xylene, 1,2-dichloroethane, chloroform) at temperatures ranging from about 40 to 120°C. Phosgene or an equivalent compound thereof is employed in an amount ranging from about 0.5 to 2 equivalents, preferably from about 0.9 to 1.1 equivalent). The reaction time ranges from several minutes to several days, preferably from about 15 minutes to about two days. The addition reaction of amine is conducted in a solvent which does not affect adversely the reaction (e.g. pyridine, tetrahydrofuran, dioxane, benzene, dichloromethane, 1,2-dichloroethane, toluene, xylene) at temperatures ranging from about 15 to 130°C. Amine is employed in an amount ranging from about 1 to 5 equivalents, preferably from about 1.1 to 3 equivalents. The reaction time ranges from several minutes to several days, preferably from about 15 minutes to about two days.

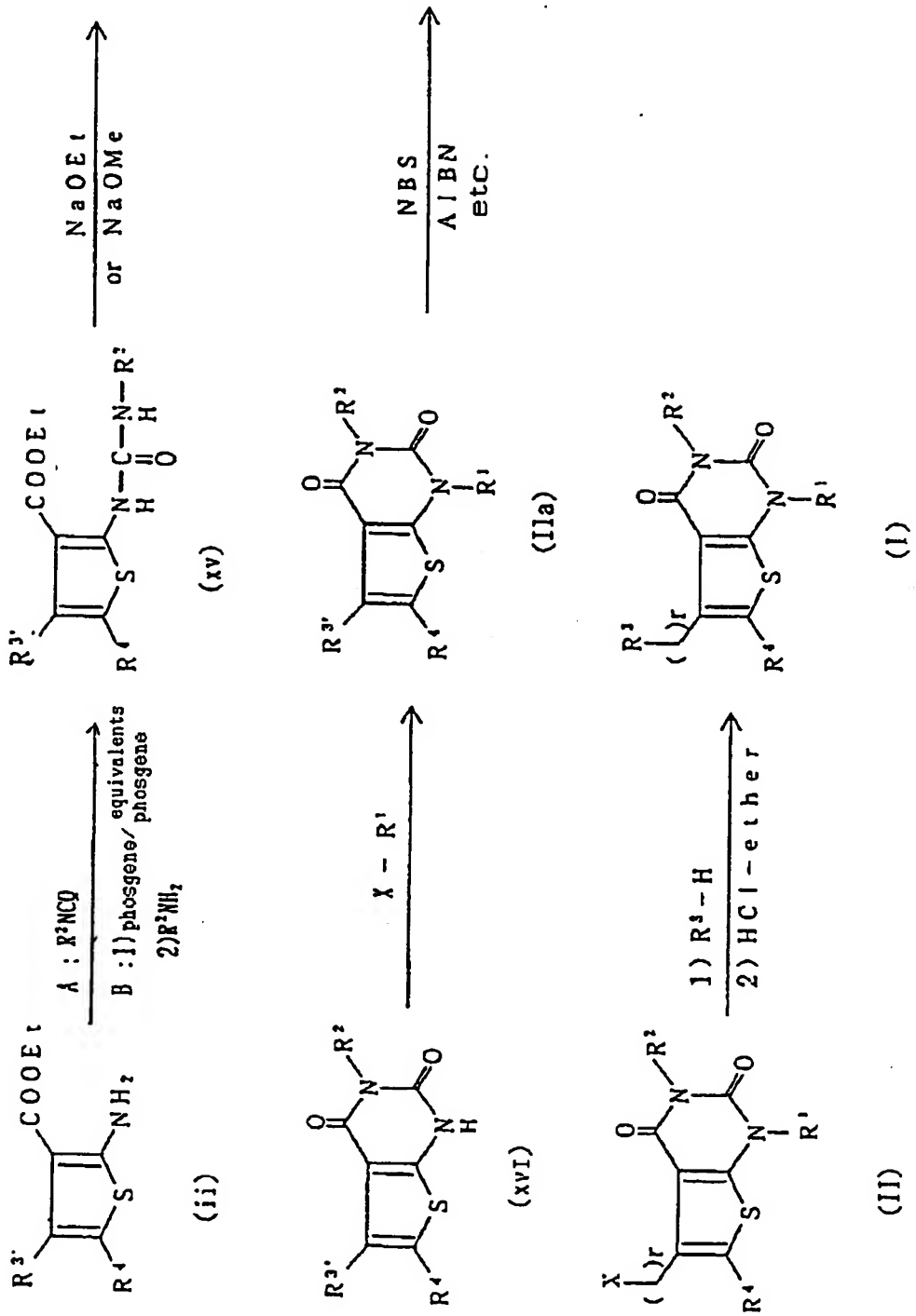
The compound (XV) or a salt thereof thus produced is processed with a base to cause ring-closure reaction to thereby produce a thieno [2,3-d] pyrimidine derivative (XVI). The ring-closure reaction is conducted in a solvent which does not affect adversely the reaction. The solvent is exemplified by alcohols such as methanol, ethanol or propanol, and ethers such as dioxane or tetrahydrofuran. As the base, use is made of, for example, an alkali metal alkoxide such as sodium methylate, sodium ethylate or sodium isopropoxide, and an alkali metal hydride such as sodium hydride. The amount of the base to be employed ranges from 1 to 5 equivalents, preferably from about 1.5 to 3 equivalents, relative to 1 equivalent of the compound (XV). The reaction temperature ranges from about 10°C to the boiling point of the solvent then employed, preferably from about 25°C to the boiling

point of the solvent then employed. The reaction time ranges from several minutes to several days, preferably from about 10 minutes to two days.

The compound (XVI) and a halogenated aralkyl derivative are stirred, in the presence of a base (e.g. an organic base such as pyridine or triethylamine), in a solvent which does not affect adversely the reaction (e.g. amides such as dimethylformamide or dimethylacetamide), at about 10 to 100°C, to produce a 2,4-dioxothieno[2,3-d]pyrimidine derivative (IIa). Subsequently, the compound (IIa) is stirred together with N-bromosuccinimide (NBS) in a solvent which does not affect adversely the reaction (e.g. halogenated hydrocarbons such as carbon tetrachloride or chloroform), in the presence of α, α'-azobisisobutyronitrile, to thereby produce the compound (II). Further, the compound (II) is stirred together with various amines, in the presence of a base, in a solvent which does not affect adversely the reaction (e.g. amides such as dimethylformamide or dimethylacetamide, nitriles such as acetonitrile, alcohols such as ethanol), at temperatures ranging from about 10 to 100°C for 0.5 to 8 hours, to thereby produce the compound (I). When necessary, the compound (I) is made into a corresponding salt with a suitable acid (e.g. hydrochloric acid or oxalic acid).

The foregoing production method is shown by the following scheme 1:

Scheme 1


A : R²NCO
B : 1) phosgene/ equivalents phosgene
2) R²NH₂
NaOEt
or NaOMe
NBS
AIBN
etc.
1) R³-H
2) HCl-ether
X - R¹
(ii)
(xv)
(IIa)
(I)
(xvI)
(II)

The respective groups described in the above scheme have the same meaning as defined above. X denotes a leaving group.

As the leaving group shown by the above X, mention is made of, for example, groups readily susceptible to substitution reaction by a nucleophilic reagent (e.g. the hydrocarbon residue having a hetero-atom with negative electric charge (e.g. oxygen atom,sulfur atom and nitrogen atom). More specifically, for example, halogen atom (e.g. iodide, bromide, chloride), alkanoyloxy (e.g. acetoxy, alkylsulfonyloxy (e.g. methanesulfonyloxy) and alkyl-aryl sulfonyloxy (e.g. p-toluenesulfonyloxy) are mentioned.

3. Method C: In place of the production method from the compound (ii) to the compound (IIa) in the above scheme 1, any per se conventional methods can be employed for example the following processes for producing the compound (IIa) from the compound (ii). Namely, the compound (ii) is dissolved in an appropriate solvent, e.g. methanol, ethanol, which does not adversely affect the reaction, 2N sodium hydroxide is added, and the mixture is reacted at room tempereture to heating (till about 100°C) for one to 12 hours. The obtained compound wherein -COOEt is converted to -COOH is dissolved in an appropriate solvent, e.g. dioxane, and to the solution is added an equivalent amount of triphosgene and the mixture is reacted at a temperature of 80 to 150°C for one to 10 hours under stirring. The obtained 1-hydroxy oxazine compound is treated in a manner similar to that of the reaction of the compound (XVI) to the compound (IIa) as mentioned above. Thus obtained oxazine compound to which the group R^1 is introduced at 1-position is dissolved in an appropriate solvent, e.g. dichloromethane, to the solution is added an equivalent amount to a small excess amount of an amine, e.g. ammonium, alkylamine, arylamine, and the

mixture is reacted at a room temperature to heating (till 100°C) for 1 to 12 hours under stirring. Then, to the reaction mixture is added triphosgene again and triethylamine as a base, the mixture is reacted at about 100°C under reflux for 1 to 6 hours, to give a compound of the formula (IIa).

4. Other methods:

The substituents on the compound (I) can be converted to other substituents by per se known and conventional methods. Examples of the methods are shown below.

(i) The nitro group as the substituent can be converted to an amino group when the starting compound is dissolved in an appropriate solvent, e.g. ethanol, methanol, and (a) to the solution is added palladium-carbon, and the mixture is reacted at room temperature for one to 12 hours under the hydrogen atmosphere, or (b) to the solution is added iron powder and hydrochloric acid, and the mixture is reacted at room temperature for one to 12 hours.

(ii) The amino group can be converted to an acylated amino group in that the starting compound is dissolved in an appropriate solvent, e.g. tetrahydrofuran, dimethylsulfoxide, to the solution is added potassium carbonate, pyridine and triethylamine as a base and acid anhydride or acid halide. The mixture is reacted at a room temperature for one to 10 hours under stirring.

(iii) From an amino compound, a compound having the amino group is converted to alkenyl-amino compound. For example, the starting compound is dissolved in an appropriate solvent, e.g. acetic acid, dimethylformamide, dichloromethane, tetrahydrofuran, dioxane, acetonitrile, to the solution is added diazonizing agent, e.g. sodium nitrite, isoamyl nitrite, to the mixture is added palladium catalyst,

e.g. bis(dibenzylideneacetone)palladium and one to excess equivalents of alkenyl derivative, and the mixture is stirred at room temperature to heating (80°C) for one to 12 hours.

(iv) A carbon atom can be introduced to the amino group, for example, to the starting compound in an appropriate solvent, e.g. acetic acid, dimethylformamide, dichloromethane, tetrahydrofuran, dioxane, is added an acrylic acid derivative or oxirane derivative, e.g. epoxide compound. The mixture is stirred at 0 to 80°C for 6 to 24 hours.

(v) A sulfur atom can be introduced to the amino group in the compound, for example, to the starting compound in an appropriate solvent, e.g. pyridine, dimethylformamide, dichloromethane, tetrahydrofuran, ethylether, dioxane, is added halide of sulfur compound. The mixture is stirred at 0 to 80°C for 6 to 24 hours.

(vi) The substituent, formyl group, can be converted to methyl group in that a starting compound is dissolved in an appropriate solvent, e.g. tetrahydrofuran, and to the mixture is added an organic borane, derivative, e.g. dimethylsulfide borane, and the mixture is reacted at room temperature to heating under reflux for a several hours, e.g. one to 3 hours.

(vii) From methoxy derivative, actonyloxy derivative can be prepared in that the starting material is dissolved in an appropriate solvent, e.g. dichloromethane, to the solution is added one to excess equivalents of Lewis acid, e.g. aluminium chloride, and thiol compound or sulfide compound (e.g. dimethylsulfide), and the mixture is reacted at ice-cooling to room temperature for one to 10 hours, and then the obtained hydroxy derivative is dissolved in an appropriate solvent, e.g. dimethylformamide, to the solution is added a base, e.g. sodium hydroxide or

potassium carbonate, and an alkyl halide. The mixture is reacted at a room temperature for one to 12 hours.
(viii) A group of methoxy can be changed to isopropoxy in that the starting material is dissolved in an appropriate solvent, e.g. dichloromethane, to the solution is added one to excess equivalents of Lewis acid, e.g. aluminum chloride, and thiol compound or sulfide compound, e.g. dimethylsulfide, and the mixture is reacted at room temperature to ice-cooling for one to 10 hours.
(ix) An aminocarbonyl group can be introduced in that a starting compound having halogen atom is dissolved in an appropriate solvent, e.g. dimethoxyethane, to the solution is added arylborric acid derivative, a base, e.g. sodium carbonate, a palladium compound e.g. tetrakis(triphenylphosphine)palladium(0), as a catalyst and the mixture is refluxed 1 to 6 hours.
(x) An alkylthio compound can be converted to an alkylsulfinyl compound or an alkylsulfonyl compound by reacting a starting compound with an oxidizing agent, e.g. metachloroperbenzoic acid, in an appropriate solvent, e.g. dichloromethane, at ice-cooling to heating. When heating harder or treating with an excess amount of oxidizing agent, an alkylsulfonyl compound is obtained.

As salts of the compounds (I) of this invention obtained thus above, physiologically acceptable acid addition salts are preferable. Examples of such salts include those with an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid) or those with an organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, bezenesulfonic acid, and p-toluenesulfonic acid).
Further, when the compound (I) of this invention has an

acid group such as -COOH, the compound(I) may form a salt with an inorganic base (e.g. an alkali metal or alkaline earth metal such as sodium, potassium, calcium and magnesium; ammonia) or an organic base (e.g. trimethylamine, triethylamine, pyridine, picolin, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine).

The compounds (I) or salts thereof of the present invention produced above can be isolated and purified by a conventional separating means such as recrystallization, distillation and chromatography. In the case where the compound (I) is produced in the free form, it can be converted to a salt thereof by a per se conventional means or a method analogous thereto. On the contrary, when it is obtained in the form of a salt, it can be converted to its free form or to any other salt.

In the case where the compound (I) or a salt thereof of the present invention is an optically active compound, it can be separated into d-form and l-form by means of a conventional optical resolution.

Since the compounds (I) of this invention have a GnRH antagonistic activity and low in toxicity, they can be safely used for the therapy of male hormone or female hormone dependent diseases as well as the therapy of diseases caused by excess secretion of these hormones, in mammalian animals (e.g. human, monkey, cow, horse, dog, cat, rabbit, rat, mouse, etc.), suppressing the secretion of gonadotropic hormone by the action of GnRH receptor antagonistic action. More specifically, the compounds of this invention are effective as a prophylactic or therapeutic agent for the prevention or treatment of several hormone dependent diseases, for example, a sex hormone dependent cancer (e.g. prostate cancer, cancer of the uterine cervix, breast cancer, pituitary adenoma),

benign prostatic hypertrophy, myoma of the uterus, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, polycystic ovary syndrome and acne vulgaris. And, the compounds of this invention are also effective as a fertility controlling agent in both sexes (e.g. pregnancy controlling agents and menstrual cycle controlling agents). The compounds of this invention can be further used as a contraceptive of male or female and, as an ovulation-inducing agent of female. The compound of this invention can be used as an infertility treating agent by using a rebound effect owing to a stoppage of administration thereof. Further, the compounds of this invention are useful as modulating estrous cycles in animals in the field of animal husbandry, and as an agent for improving the quality of edible meat or promoting the growth of animals. Besides, the compounds of this invention are useful as an agent of spawning promotion in fish. While the compounds of this invention can be used singly, they can also effectively be used by administering in combination with a steroidal or non-steroidal antiandrogenic agent. The compound of this invention can be used for the suppressing a passing ascent of testosterone concentration in plasma, the ascent which occurs in administration of GnRH super antagonist such as leuprorelin acetate. The compound of this invention can effectively be used by administering in combination with a chemoterapeutic agent for cancer. In treatment of prostate cancer, examples of the chemoterapeutic agent include Ifosfamide, UFT, Adriamycin, Peplomycin, Cisplatin and the like. In treatment of breast cancer, examples of the chemoterpeutic agent include Cyclophohamide, 5-FU-, UFT, Methotrexate, Adriamycin, Mitomycin C, Mitoxantrone and the like.

The present compounds (I) shows sufficient GnRH

activity through subcutaneous or oral administration, is stably absorbed through oral administration and shows GnRH activity over a long time.

When the compound (I) of this invention is employed, in the field of animal husbandry or fisheries, as prophylactic and therapeutic agents of the above-mentioned diseases, is can be administered orally or non-orally in accordance with per se known means. It is mixed with a pharmaceutically acceptable carrier and usually administered orally as a solid preparation such as tablet, capsule, granule or powder, or non-orally as intravenous, subcutaneous or intramuscular injection, or as suppository or sublingually administrable tablet. Further, it is sublingually, subcutaneously or intramuscularly administered as a prolonged release formulation such as sublingually administrable tablets, or microcapsules. The daily dose of the present compound (I) varies with the degree of affliction; age, sex, body weight and difference of sensitivity of the subject to be administered; the time and intervals of administration, properties, dosage forms and kinds of the medicinal preparation; and kinds of the effective components, and it ranges usually, though not specifically limited, from about 0.01 to 10 mg, preferably from about 0.02 to 2 mg, more preferably from about 0.01 to 1 mg, relative to 1 kg body weight of mammalian animals, which is administered usually once daily or by 2 to 4 divided dosages. The daily dose when used in the field of animal husbandry or fishery varies with the conditions analogous to those mentioned above, it ranges, relative to 1 kg body weight of the subject animal or fish, from about 0.001 to 5 mg, preferably from about 0.002 to 2 mg, once or 2 to 3 divided dosages.

As the above-mentioned pharmaceutically acceptable carriers, conventional various organic or inorganic

carriers are used, and they are incorporated as excipients, lubricants, binders and disintegrants in solid compositions; and as solvents, solubilisers, suspending agents, isotonizing agents, buffering agents and pain-easing agents in liquid compositions. And, depending on necessity, further additives such as preservatives, anti-oxidants, coloring agents and sweeteners can also be used.

Preferable examples of the above-mentioned excipients include lactose, sugar, D-mannito, starch, crystalline cellulose and more volatile silicon dioxide. Preferable examples of above-mentioned lubricants include magnesium stearate, calcium stearate, talc and colloid silica. Preferable examples of the above-mentioned binders include crystalline cellulose, sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxymethyl cellulose and polyvinyl pyrrolidone. Preferable examples of the above-mentioned disintegrants include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, cross carmelose sodium, cross carmelose sodium and carboxymethyl starch sodium. Preferable examples of the above-mentioned solvents include water for injection, alcohol, propylene glycol, macrogol, sesame oil and corn oil. Preferable examples of the above-mentioned solubilizers include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, tris-aminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate. Preferable examples of the above-mentioned suspending agents include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, lauryl aminopropionic acid, lecithin, benzalkonium chloride, benzetonium chloride and monostearic glyceryl ester; and hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, methyl cellulose,

hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose. Preferable examples of the above-mentioned isotonizing agents include sodium chloride, glycerin and D-mannitol. Preferable examples of the above-mentioned buffering agents include buffer solutions such as phosphate, acetate, carbonate and citrate. Preferable examples of the above-mentioned pain-easing agents include benzyl alcohol. Preferable examples of the above-mentioned preservatives include para-hydroxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid. Preferable examples of the above-mentioned anti-oxidants include sulfite and ascorbic acid.

To the compound (I) of this invention, are added, for example, a suspending agent, a solubilizer, a stabilizer, an isotonizing agent and a preservative, then the mixture is formulated, in accordance with a per se known method, into an intravenous, subcutaneous or intramuscular injection. These injections can be processed into lyophilized preparations, when necessary, by a per se known method.

Examples of the above-mentioned pharmaceutical composition are oral agents (e.g. diluted powders, granules, capsules and tablets), injections, dropping injections, external agents (e.g. transnasal preparations, percutaneous preparations, etc.), ointments (e.g. rectal ointment, vaginal ointment, etc.) and the like.

Such pharmaceutical compositions can be manufactured by a per se known method commonly used in preparing pharmaceutical compositions.

The compound (I) of the present invention or a salt thereof can be made into injections either in a form of an aqueous injection together with dispersing agents [e.g. Tween 80 (Atlas Powder, U.S.A.), HCO 80

(Nikko Chemicals, Japan), polyethylene glycol, carboxymethylcellulose, sodium alginate, etc.], preservatives (e.g. methyl paraben, propyl paraben, benzyl alcohol, etc.), isotonizing agents (e.g. sodium chloride, mannitol, sorbitol, glucose, etc.) and the like or in a form of an oily injection by dissolving, suspending or emulsifying in plant oil (e.g. olive oil, sesame oil, cotton seed oil, corn oil, etc.), propylene glycol and the like.

In preparing a pharmaceutical composition for oral use, the compound (I) of the present invention or a salt thereof is molded by compressing, for example, with fillers (e.g. lactose, sucrose, starch, etc.), disintegrating agents (e.g. starch, calcium carbonate, etc.), binders (e.g. starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.) or lubricants (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.) and the like. If necessary, the composition is coated by a per se known method with an object of masking the taste, enteric coating or long-acting. Examples of the coating agent therefore are hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, Tween 80, pluronic F 68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (a copolymer of methacrylic acid with acrylic acid; manufactured by Rohm, Germany), red oxide of iron and the like. Subcoating layer may be provided between the enteric coating and the core according to per se known method.

In preparing an external composition, the compound (I) of the present invention or a salt thereof as it is or a salt thereof is subjected to a per se known method

to give a solid, semisolid or liquid agent for external use. For example, the solid preparation is manufactured as follows. Thus, the compound of the present invention as it is or after adding/mixing fillers (e.g. glycol, mannitol, starch, microcrystalline cullulose, etc.), thickeners (e.g. natural gums, cellulose derivatives, acrylic acid polymers, etc.) and the like thereto/therewith is made into a powdery composition. With respect to the liquid composition, an oily or aqueous suspension is manufactured by the manner nearly the same as in the case of the injection. In the case of a semisolid composition, the preferred one is an aqueous or oily gel or an ointment. Each of them may be compounded with a pH adjusting agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), an antiseptic agent (e.g. p-hydroxybenzoates, chlorobutanol, benzalkonium chloride, etc.) and the like.

In the manufacture of an ointment for example, the compound (I) of the present invention or a salt thereof can be made into an oily or an aqueous solid, semisolid or liquid ointment. Examples of the oily base material applicable in the above-mentioned composition are glycerides of higher fatty acids [e.g. cacao butter, Witepsols (manufactured by Dynamite-Nobel), etc.], medium fatty acids [e.g. Miglyols (manufactured by Dynamite-Nobel), etc.] and plant oil (e.g. sesame oil, soybean oil, cotton seed oil, etc.) and the like. Examples of the aqueous base material are polyethylene glycols and propylene glycol and those of the base material for aqueous gel are natural gums, cellulose derivatives, vinyl polymers, acrylic acid polymers, etc.

Best Mode for Carrying Out of the Invention

By way of the following Reference Examples and Working Examples, the present invention will be described more specifically, but they are not intended to limit the scope of this invention thereto.

^{1}H-NMR spectra were taken with the Varian GEMINI 200 (200 MHz) type spectrometer, JEOL LAMBDA300 (300MHz) type spectrometer or the Brucker AM 500 (500 MHz) type spectrometer, employing tetramethylsilane as the internal standard. All delta values were expressed in ppm.

The symbols used in the present specification have the following meanings:

s: singlet, d: doublet, t: triplet, dt: double triplet, m: multiplet, br: broad

Reference Example 1

Production of 2-amino-5-phenylthiophene-3-carboxylic acid ethyl ester:

To a mixture of ethyl cyanoacetate (6.1 g, 50 mmol), sulfur (1.61 g, 50 mmol) triethylamine (3.5 ml, 25 mmol) and dimethylformamide (10 ml) was added dropwise, with stirring at 45°C, phenylacetaldehyde (50% diethylphthalate solution; 12.05 g, 50 mmol) for 20 minutes. The mixture was stirred for 9 hours at 45°C, and the reaction mixture was concentrated. The resulting residue was extracted with ethylacetate. The extract was washed with an aqueous sodium chloride solution, which was then dried ($MgSO_4$), followed by distilling off the solvent under reduced pressure. The residue was chromatographed on silica gel, followed by crystallization from ether-hexane to give slightly yellow plates (5.55 g, 45%), m.p.124.5-125.5°C (value in literature reference 123-124°C).

Elemental Analysis for $C_{13}H_{13}NO_2S$:

	C(%)	H(%)	N(%)
Calcd.:	63.13 ;	5.30 ;	5.66
Found :	62.99 ;	5.05 ;	5.63

^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.37(3H,t,J=7.1Hz), 4.30(2H,d,J=7.1Hz), 5.97(2H,br), 7.17-7.46(6H,m).

IR(KBr): 3448, 3320, 1667, 1590, 1549 cm^{-1}.

Reference Example 2

Production of 2-amino-4-methyl-5-(4-methoxyphenyl)thiophene-3-carboxylic acid ethyl ester:

A mixture of 4-methoxyphenylacetone (16.5 g, 0.10 mol), ethyl cyanoacetate (12.2 g, 0.10 mol), ammonium acetate (1.55 g, 20 mmol), acetic acid (4.6 ml, 80 mmol) and benzene (20 ml) was heated for 24 hours under reflux, while removing water produced in the reaction mixture using a Dean and Stark apparatus. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between dichloromethane and an aqueous sodium hydrogencarbonate solution. The organic layer was washed with an aqueous sodium chloride solution, which was then dried ($MgSO_4$), followed by distilling of the solvent under reduced pressure. To an ethanol (30 ml) solution of the residue were added sulfur (3.21 g, 0.10 mol) and diethylamine (10.4 ml, 0.10 mol). The mixture was stirred at 50-60°C for 2h and then concentrated, and the concentrate was extracted with ethyl acetate. The extract was washed with an aqueous sodium chloride solution and dried ($MgSO_4$), followed by distilling off the solvent under reduced pressure. The residue was chromatographed on silica gel, which was the crystallized from ether-hexane to give a pale yellow plates (11.5 g, 40%), m.p.79-80°C.

Elemental Analysis for $C_{15}H_{17}NO_3S$:

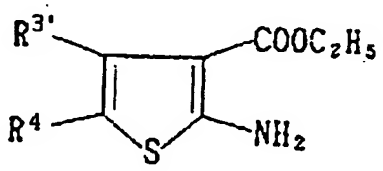
	C(%)	H(%)	N(%)	S(%)
Calcd.:	61.83 ;	5.88 ;	4.81 ;	11.01
Found :	61.81 ;	5.75 ;	4.74 ;	10.82

^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.37(3H,t,J=7.1Hz), 2.28(3H,s), 3.83(3H,s), 4.31(2H,q,J=7.1Hz), 6.05(2H,brs), 6.91(2H,d,J=8.8Hz), 7.27(2H,d,J=8.8Hz).
IR(KBr): 3426, 3328, 1651, 1586, 1550, 1505, 1485 cm^{-1}.
FAB-MS m/z: 291 (M^+)

Reference Example 3

Employing various acetone derivatives in place of 4-methoxyphenylacetone, compounds shown in Table 1 are produced in accordance with substantially the same manner as described in Reference Example 2.

Table 1



Ref.Ex. 3 Cpd.No.	$R^{3'}$	R^4	Yield (%)	m.p. (°C)
1	methyl	phenyl	40	64-65
2	methyl	2-methoxyphenyl	12	70-71
3	methyl	brom		

Reference Example 4

Production of 2-amino-4-methyl-5-(4-nitrophenyl)thiophene-3-carboxylic acid ethyl ester:

In substantially the same procedure as described in Reference Example 1, using 4-nitrophenylacetone (35.0 g, 195 mmol) in place of 4-methoxyphenyl acetone, ethyl cyanoacetate (23 g, 19.5 mmol), ammonium acetate (3.1 g, 40 mmol), acetic acid (9.1 ml, 159 mmol), sulfur (5.0 g, 160 mmol) and diethylamine (16.0 ml, 160 mmol), the titled compound was produced as colorless crystals (22.2 g, 52%). m.p.168-170°C (recrystallized from ether-hexane).

Elemental Analysis for $C_{14}H_{14}N_2O_4S$:

	C(%)	H(%)	N(%)
Calcd.:	54.89 ;	4.61 ;	9.14
Found :	54.83 ;	4.90 ;	9.09

^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.39(3H,t,J=7.1Hz), 2.40(3H,s), 4.34(2H,q,J=7.1Hz), 6.27(2H,brs), 7.48(2H,d,J=8.7Hz), 8.23(2H,d,J=8.7Hz).

IR (KBr): 3446, 3324, 1667, 1580, 1545, 1506, 1491, 1475, 1410, 1332 cm^{-1}.

Reference Example 5

Production of 2,4(1H,3H)-dioxo-5-methyl-6-(4-methoxyphenyl)-thieno[2,3-d]pyrimidin-3-acetic acid ethyl ester:

To a solution of the compound produced in Reference Example 1 (5.00 g, 17.20 mmol) was added ethyl isocyanatoacetate (2.90 ml, 25.80 mmol). The mixture was stirred for 6 hours at 45°C, followed by concentration under reduced pressure. The concentrate was dissolved in ethanol (6 ml), to which was added sodium ethoxide {prepared from ethanol (30 ml) and sodium (0.79 g, 34.30 mmol)}. The mixture was stirred for 24 hours at room temperature, to which was added 2N HCl (18 ml, 36 mmol). Ethanol was distilled off under reduced pressure, and the residue was subjected to filtration, which was washed with water-ethanol and dried under reduced pressure, followed by recrystallization from ethanol to give white needles (5.70 g, 89%). m.p.164-165°C.

Elemental Analysis for $C_{18}H_{18}N_2O_5S$:

	C(%)	H(%)	N(%)
Calcd.:	57.74 ;	4.85 ;	7.48
Found :	57.78 ;	5.03 ;	7.45

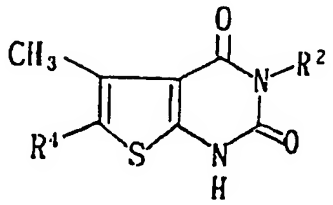
^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.30(3H,t,J=7.2Hz), 2.45(3H,s), 3.85(3H,s), 4.26(2H,q,J=7.2Hz), 4.78(2H,s), 6.95(2H,d,J=8.8Hz), 7.31(2H,d,J=8.8Hz), 10.58(1H,s).

IR (KBr): 2914, 1742, 1713, 1655, 1605, 1568, 1528, 1499 cm^{-1}.

Reference Example 6

Employing, as starting materials, the compounds which are produced in Reference Examples 2, 3 or 4, compounds which are produced in accordance with the method described in Reference Example 5 are set forth in Table 2.

Table 2



Ref.Ex. 6 Cpd.No.	R^2	R^4	Yield (%)	m.p. (°C)
1	(ethoxycarbonyl) methyl	phenyl	85	119-120
2	methyl	4-methoxy-phenyl	84	273-276
3	phenyl	4-methoxy-phenyl	85	>300
4	phenyl	4-nitro-phenyl	84	>300
5	benzyl	4-methoxy-phenyl	92	241-242
6	4-methoxyphenyl	4-methoxy-phenyl	99	>300
7	cyclohexyl	4-methoxy-phenyl	84	275-276
8	2-methoxyphenyl	4-methoxy-phenyl	81	257-258
9	3-methoxyphenyl	4-methoxy-phenyl	93	>300
10	2-chlorophenyl	4-methoxy-phenyl	95	285-286
11	3-chlorophenyl	4-methoxy-phenyl	97	>300
12	4-chlorophenyl	4-methoxy-phenyl	95	>300

Ref.Ex. 6 Cpd.No.	R^2	R^4	Yield (%)	m.p. (°C)
13	3-methoxyphenyl	bromo	100	245-247
14	3-isopropoxy-phenyl	bromo		
15	3-isopropoxy-phenyl	4-methoxy-phenyl		
16	3-methoxy-methoxyphenyl	4-nitro-phenyl	86	263-267

Reference Example 7

Production of 2,4(1H,3H)-dioxo-6-(4-nitrophenyl)-5-methylthieno[2,3-d]pyrimidin-3-acetic acid ethyl ester:

To the compound 1 produced in Reference Example 6 (2.20 g, 6.39 mmol) was added conc. sulfuric acid (12 ml). To the mixture was added dropwise, under ice-cooling, a solution of sodium nitrate (550 mg, 6.47 mmol) in conc. sulfuric acid, followed by stirring for one hour under ice-cooling. The reaction mixture was poured into ice-water, which was extracted with ethyl acetate. The extract was washed with an aqueous sodium chloride solution and dried ($MgSO_4$), followed by distilling off the solvent under reduced pressure. The residue was chromatographed on silica gel to give a yellowish solid (1.30 g, 52%), which was then recrystallized from ethyl acetate - hexane to yellow crystals, m.p.277-280°C.

Elemental Analysis for $C_{17}H_{15}N_3O_6S \cdot 0.4H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	51.48 ;	4.01 ;	10.59
Found :	51.64 ;	3.79 ;	10.61

^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.33(3H,t,J=7.2Hz), 2.56(3H,s), 4.28(2H,q,J=7.2Hz), 4.79(2H,s), 7.57(2H,d,J=8.8Hz), 8.30(2H,d,J=8.8Hz), 10.30(1H,s).

IR (KBr): 1748, 1719, 1663, 1522, 1460 cm^{-1}.

Reference Example 8

Production of 2,4(1H,3H)-dioxo-1-(2-fluorobenzyl)-6-(4-nitrophenyl)-5-methylthieno[2,3-d]pyrimidin-3-acetic acid ethyl ester:

To a solution of the compound produced in Reference Example 7 (700 mg, 1.80 mmol) in dimethylformamide (10 ml) were added potassium carbonate (372 mg, 2.70 mmol), potassium iodide (299 mg, 1.80 mmol) and 2-fluorobenzyl chloride (0.43 ml, 3.60 mmol). The mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated, and the concentrate was partitioned between ethyl acetate and an aqueous sodium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined extract was washed with an aqueous sodium chloride solution, which was then dried ($MgSO_4$), followed by distilling off the solvent under reduced pressure. The residue was chromatographed on silica gel to give a white powder (500 mg, 56%).
m.p.155-158°C.

Elemental Analysis for $C_{24}H_{20}N_3O_6SF \cdot 0.5H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	56.91 ;	4.18 ;	8.30
Found :	56.74 ;	3.84 ;	8.25

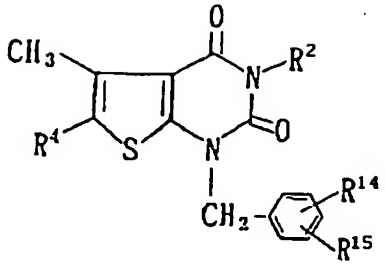
^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.32(3H,t,J=7.2Hz), 3.84(3H,s), 4.27(2H,q,J=7.2Hz), 4.84(2H,s), 5.30(2H,s), 7.06-7.33(4H,m), 7.54(2H,d,J=8.9Hz), 7.27(2H,d,J=8.9Hz).

IR (KBr): 1748, 1711, 1673, 1520, 1491 cm^{-1}.

Reference Example 9

Starting from the compounds which are produced in Reference Example 6, compounds which are produced in accordance with the method described in Reference Example 8 are set forth in Table 3.

Table 3



Ref.Ex.9 Cpd.No.	R^2	R^{14}, R^{15}	R^4	Yield (%)	m.p. (°C)
1	(ethoxycarbonyl) methyl	2-fluoro	4-methoxy-phenyl	87	127-128
2	methyl	2-methoxy	4-methoxy-phenyl	92	174-175
3	methyl	2-fluoro	4-methoxy-phenyl	97	179-180
4	phenyl	2-methoxy	4-methoxy-phenyl	93	240-241
5	phenyl	2-fluoro	4-methoxy-phenyl	96	252-253
6	phenyl	2-fluoro	4-nitro-phenyl	87	294-295
7	phenyl	3-fluoro	4-methoxy-phenyl	88	215-217
8	phenyl	4-fluoro	4-methoxy-phenyl	66	209-212
9	phenyl	2,4-difluoro	4-methoxy-phenyl	73	227-228
10	phenyl	2,6-difluoro	4-methoxy-phenyl	87	291-292
11	phenyl	2-chloro, 6-fluoro	4-methoxy-phenyl	91	287-288
12	phenyl	2-methyl-thio	4-methoxy-phenyl	81	239-240
13	benzyl	2-fluoro	4-methoxy-phenyl	86	124-126
14	benzyl	2,6-difluoro	4-methoxy-phenyl	82	161-163
15	4-methoxyphenyl	2-fluoro	4-methoxy-phenyl	87	270-272
16	4-methoxyphenyl	2,6-difluoro	4-methoxy-phenyl	83	>300
17	cyclohexyl	2-fluoro	4-methoxy-phenyl	79	172-173
18	cyclohexyl	2,6-difluoro	4-methoxy-phenyl	73	207-208

Ref.Ex.9 Cpd.No.	R^2	R^{14}, R^{15}	R^4	Yield (%)	m.p. (°C)
19	phenyl	2,6-difluoro	4-nitro-phenyl	93	280-282
20	2-methoxyphenyl	2-fluoro	4-methoxy-phenyl	84	195-198
21	2-methoxyphenyl	2,6-difluoro	4-methoxy-phenyl	86	205-208
22	3-methoxyphenyl	2-fluoro	4-methoxy-phenyl	89	241-242
23	3-methoxyphenyl	2,6-difluoro	4-methoxy-phenyl	85	253-255
24	2-chlorophenyl	2-fluoro	4-methoxy-phenyl	91	220-221
25	2-chlorophenyl	2,6-difluoro	4-methoxy-phenyl	83	178-182
26	3-chlorophenyl	2-fluoro	4-methoxy-phenyl	90	247-248
27	3-chlorophenyl	2,6-difluoro	4-methoxy-phenyl	93	278-279
28	4-chlorophenyl	2-fluoro	4-methoxy-phenyl	79	269-270
29	4-chlorophenyl	2,6-difluoro	4-methoxy-phenyl	91	>300
30	3-methoxyphenyl	2,6-difluoro	bromo	89	261-262
31	3-isopropoxy-phenyl	2,6-difluoro	bromo		
32	3-isopropoxy-phenyl	2,6-difluoro	4-methoxy-phenyl		

Reference Example 10

Production of 5-bromomethyl-2,4(1H,3H)-dioxo-1-(2-fluorobenzyl)-6-(4-nitrophenyl)thieno[2,3-d]pyrimidin-3-acetic acid ethyl ester:

A mixture of the compound produced in Reference Example 8 (0.300 g, 0.603 mmol), N-bromosuccinimide (0.107 g, 0.603 mmol), α,α'-azobisisobutyronitrile (10 mg, 0.60 mmol) and carbon tetrachloride (15 ml) was refluxed for 2 hours. Upon cooling resulting insolubles were filtered off from the reaction mixture. The filtrate was diluted with chloroform. The organic layer was washed with an aqueous sodium chloride

solution and dried ($MgSO_4$), then the solvent was distilled off under reduced pressure. The residue was recrystallized from ethyl acetate to give colorless needles (0.284 g, 82%), m.p.165-167°C.

Elemental Analysis for $C_{24}H_{19}N_3O_6SBrF$:

	C(%)	H(%)	N(%)
Calcd.:	50.01 ;	3.32 ;	7.29
Found :	49.87 ;	3.27 ;	7.23

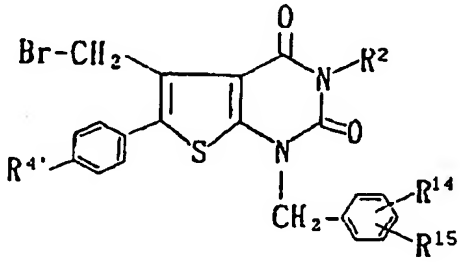
^{1}H-NMR (200MHz, $CDCl_3$) δ: 1.31(3H,t,J=7.1Hz), 4.26(2H,q,J=7.1Hz), 4.78(2H,s), 4.86(2H,s), 5.30(2H,s), 7.07-7.37(4H,m), 7.75(2H,d,J=8.8Hz), 8.33(2H,d,J=8.8Hz).

IR (KBr): 1713, 1673, 1524, 1477 cm^{-1}.

Reference Example 11

Starting from the compounds which is produced in Reference Example 9, compounds which are produced in accordance with the method described in Reference Example 10 are set forth in Table 4. The compounds 30 to 33 is produced from the compounds 30 or 31 of Reference Example 9 by the method of Example 18.

Table 4



Ref.Ex.11 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	Yield (%)	m.p. (°C)
1	(ethoxy-carbonyl)-methyl	2-fluoro	methoxy	70	152-153
2	methyl	2-methoxy	methoxy	63	173-176
3	methyl	2-fluoro	methoxy	82	175-177
4	phenyl	2-methoxy	methoxy	93	240-241
5	phenyl	2-fluoro	methoxy	86	230-233

Ref.Ex.11 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	Yield (%)	m.p. (°C)
6	phenyl	2-fluoro	nitro	86	224-225
7	phenyl	3-fluoro	methoxy	84	215-216
8	phenyl	4-fluoro	methoxy	84	232-233
9	phenyl	2,4-difluoro	methoxy	84	230-231
10	phenyl	2,6-difluoro	methoxy	87	250-252
11	phenyl	2-chloro, 6-fluoro	methoxy	86	255-257
12	phenyl	2-methyl-thio	methoxy	90	212-214
13	benzyl	2-fluoro	methoxy	83	132-134
14	benzyl	2,6-difluoro	methoxy	89	154-155
15	4-methoxy phenyl	2-fluoro	methoxy	88	226-228
16	4-methoxy phenyl	2,6-difluoro	methoxy	80	249-251
17	cyclohexyl	2-fluoro	methoxy	86	149-151
18	cyclohexyl	2,6-difluoro	methoxy	77	192-194
19	phenyl	2,6-difluoro	nitro	94	228-229
20	2-methoxy-phenyl	2-fluoro	methoxy	77	180-181
21	2-methoxy-phenyl	2,6-difluoro	methoxy	79	212-214
22	3-methoxy-phenyl	2-fluoro	methoxy	82	234-235
23	3-methoxy-phenyl	2,6-difluoro	methoxy	88	255-256
24	2-chloro-phenyl	2-fluoro	methoxy	85	175-178
25	2-chloro-phenyl	2,6-difluoro	methoxy	88	191-193
26	3-chloro-phenyl	2-fluoro	methoxy	81	243-246
27	3-chloro-phenyl	2,6-difluoro	methoxy	92	270-273
28	4-chloro-phenyl	2-fluoro	methoxy	84	271-274
29	4-chloro-phenyl	2,6-difluoro	methoxy	78	265-268

Ref.Ex.11 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	Yield (%)	m.p. (°C)
30	3-methoxy-phenyl	2,6-difluoro	propylamino-carbonyl		
31	3-methoxy-phenyl	2,6-difluoro	isopropyl-aminocarbonyl		
32	3-isopropoxy-phenyl	2,6-difluoro	propylamino-carbonyl		
33	3-isopropoxy-phenyl	2,6-difluoro	isopropyl-aminocarbonyl		
34	3-isopropoxy-phenyl	2,6-difluoro	methoxy		

Reference Example 12

Production of 5-(N-benzyl-N-methylaminomethyl)-2,4(1H,3H)-dioxo-1-(2-fluorobenzyl)-6-(4-nitrophenyl)thieno[2,3-d]pyrimidin-3-acetic acid ethyl ester hydrochloride:

To a solution of the compound produced in Reference Example 10 (0.270 g, 0.47 mmol) in dimethylformamide (10 ml) were added, under ice-cooling, ethyl diisopropylamine (0.12 ml, 0.710 mmol) and benzylmethyl amine (0.07 ml, 0.56 mmol). The mixture was stirred for 20 hours at room temperature. The reaction mixture was concentrated, and the concentrate was partitioned between ethyl acetate and a saturated aqueous solution of sodium hydrogencarbonate. The aqueous layer was extracted with ethyl acetate. Organic layers were combined and dried ($MgSO_4$), then the solvent was distilled off under reduced pressure. The residue was chromatographed on silica gel to give a colorless oil (0.297 g, 100%). To a solution of this oil in ethyl acetate was added, under ice-cooling, 1N solution of hydrogen chloride in ether. The mixture was stirred for 10 minutes at the same temperature. The reaction mixture was concentrated under reduced pressure, and the concentrate was crystallized from ethyl acetate - ether to give the corresponding hydrochloride (0.084 g) as white crystals.

m.p. 120-128°C

Elemental Analysis for $C_{32}H_{29}N_4O_6SF \cdot HCl \cdot H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	57.27 ;	4.81 ;	8.35
Found :	57.23 ;	4.55 ;	8.42

IR (KBr): 1711, 1665, 1522, 1493 cm^{-1}.

Reference Example 13

Production of 3-isobutyl-2,4(1H,3H)-dioxo-5-methyl-6-(4-methoxyphenyl)thieno[2,3-d]pyrimidine:

A mixture of isovaleric acid (1.15 ml, 10.03 mmol), diphenylphosphoryl azide (2.83 g, 10.30 mmol), triethylamine (1.45 ml, 10.03 mmol) and benzene (15 ml) was heated for one and half hour under reflux, to emerge isobutyl isocyanate. To the resultant mixture, the compound produced in Reference Example 2 (2.00 g, 6.85 mmol) and benzene (5 ml) were added, and the mixture was heated under reflux for 4 days. The reaction mixture was subjected to distribution procedure with ethyl acetate and an aqueous sodium chloride solution. The water layer was extracted with ethyl acetate, and the combined extracts were washed with an aqueous sodium chloride solution and dried with $MgSO_4$, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to obtain white powders (2.64 g, 99%). The obtained urea derivative was dissolved in ethanol (30 ml), 28% sodium methoxide (3.93 g, 20.37 mmol) was added to the solution, the mixture was stirred at room temperature for 16 hours, 1N hydrochloric acid (22 ml, 22 mmol) was added. The solvent, ethanol, was distilled off under reduced pressure. The resulting residue was filtrated, washed with water-ethanol, dried under reduced pressure, and then crystallized from ethanol, to give white needles (1.61 g, 70%).

m.p. 215-216°C.

Elemental Analysis for $C_{18}H_{20}N_2O_3S$:

	C(%)	H(%)	N(%)
Calcd.:	62.77 ;	5.85 ;	8.13
Found :	62.75 ;	5.82 ;	8.04.

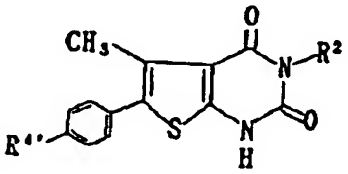
^{1}H-NMR (300MHz, $CDCl_3$) δ: 0.96(6H,d,J=6.8Hz), 2.20(1H,sept,J=6.8Hz), 2.50(3H,s), 3.85-3.87(5H,m), 6.96(2H,d,J=8.8Hz), 7.33(2H,d,J=8.8Hz), 9.50(1H,s).

IR (KBr):1711, 1657, 1537, 1499, 1458 cm^{-1}.

Reference Example 14

Employing the compounds which are produced in Reference Example 2 or 4 as a starting material, compounds which are produced in accordance with the method described in Reference Example 13 are set forth in Table 5.

Table 5



Ref.Ex. 14 Cpd.No.	R^2	$R^{4'}$	Yield (%)	m.p. (°C)
1	methoxyethyl	methoxy	95	131-233
2	3,5-dimethoxyphenyl	methoxy	87	>300
3	3,5-dimethoxyphenyl	nitro	85	>300

Reference Example 15

Production of 2-amino-4-methyl-5-(4-methoxyphenyl)thiophene-3-carboxylic acid:

To an ethanol solution (60 ml) of the compound (3.0 g, 10.3 mmol) produced in Reference Example 2, 2N sodium hydroxide (20.0 ml, 40.0 mmol) was added and the mixture was heated under reflux for 1.5 hours. After cooling, 2N hydrochloric acid (20.0 ml, 40.0 mmol) was added to the reaction mixture to neutralize the solution, and the solution was extracted with ethyl

acetate. The organic layer was washed with an aqueous sodium chloride solution, and then dried with $MgSO_4$. The solvent was distilled off under reduced pressure, and the residue was washed with ether-hexane to give pale yellowish powder (2.2 g, 91%).
m.p. 142-145°C.
^{1}H-NMR (200MHz, DMSO-d_6) δ: 2.22(3H,s), 3.79(3H,s), 6.98(2H,d,J=8.8Hz), 7.25(2H,d,J=8.8Hz), 7.39(2H,s).
IR (KBr): 3470, 1647, 1576, 1508, 1475 cm^{-1}.

Reference Example 16

Production of 2,4(1H)-dioxo-6-(4-methoxyphenyl)-5-methylthieno[2,3-d]oxazine:

To a dioxane solution (10 ml) of the compound (6.00 g, 22.8 mmol) produced in Reference Example 15, triphosgene (6.76 g, 22.8 mmol) was added, and the mixture was stirred at 100°C for 4 hours. After the reaction, the reaction solution was concentrated, then the residue was filtered and washed with ether to give pale yellowish powder (596 g, 90%) was obtained.
m.p. 209-210°C.
^{1}H-NMR (200MHz, DMSO-d_6) δ: 2.36(3H,s), 3.82(3H,s), 7.06(2H,d,J=8.8Hz), 7.41(2H,d,J=8.8Hz), 10.50(1H,s).
IR (KBr): 1779, 1709, 1533, 1497 cm^{-1}.

Reference Example 17

Production of 2,4(1H)-dioxo-1-(2-fluorobenzyl)-6-(4-methoxyphenyl)-5-methylthieno[2,3-d]oxazine:

To a dimethylformamide (30 ml) solution of the compound (4.80 g, 16.59 mmol) produced in Reference Example 16, potassium carbonate (3.43 g, 24.88 mmol), potassium iodide (2.75 g, 16.59 mmol) and 2-fluorobenzylchloride (2.96 ml, 24.88 mmol) were added, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated, the residue was subjected to distribution with ethyl acetate and an aqueous sodium chloride solution. The aqueous layer was extracted with ethyl acetate, the

extracts were combined and washed with an aqueous sodium chloride solution and dried with $MgSO_4$, and the solvent was distilled off under reduced pressure. The obtained residue was subjected to purification by silica gel column chromatography to give white crystals (4.87 g, 74%).

m.p. 162-163°C.

^{1}H-NMR (200MHz, $CDCl_3$) δ: 2.43(3H,s), 3.84(3H,s), 5.21(2H,s), 6.95(2H,d,J=8.8Hz), 7.05-7.44(6H,m).

IR (KBr): 1769, 1719, 1562, 1531, 1493 cm^{-1}.

FAB-MS m/z: 398.1(MH^+).

Reference Example 18

Production of 2,4(1H)-dioxo-1-(2,6-difluorobenzyl)-6-(4-methoxyphenyl)-5-methylthieno[2,3-d]oxazine:

In substantially the same procedure as described in Reference Example 17, using 2,6-difluorobenzylchloride (1.18 g, 7.26 mmol) in place of 2-fluorobenzylchloride, from the compound (2.00 g, 6.91 mmol) obtained in Reference Example 17, potassium carbonate (0.95 g, 6.91 mmol) and potassium iodide (1.15 g, 6.91 mmol), the titled compound was produced as colorless crystals (2.34 g, 82%).

m.p. 189-190°C (recrystallized from ethyl acetate-hexane).

^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.42(3H,s), 3.84(3H,s), 5.27(2H,s), 6.90-6.96(4H,m), 7.24-7.36(3H,m).

IR (KBr): 1775, 1731, 1528, 1468 cm^{-1}.

Reference Example 19

Production of 2,4-(1H,3H)-dioxo-1-(2-fluorobenzyl)-6-(4-methoxyphenyl)-3-(3-methoxypropyl)-5-methylthieno[2,3-d]pyrimidine:

To a dichloromethane (12 ml) solution of the compound obtained in Reference Example 17, 3-methoxypropylamine (0.17 ml, 1.67 mmol) was added under ice-cooling, and the mixture was stirred at room temperature for 1 hour. The residue obtained by

concentrating the reaction mixture was subjected to distribution with dichloromethane and an aqueous sodium chloride solution. The aqueous layer was extracted with dichloromethane, the extracts were combined, the extracts was washed with an aqueous sodium chloride solution and dried with $MgSO_4$, and then the solvent was distilled off. Thus obtained residue was purified by silica gel column chromatography to give a white powder (524 mg, 78%). The obtained amine derivative was dissolved in tetrahydrofuran (20 ml), and to this solution triphosgene (351 mg, 1.18 mmol) and triethylamine (0.15 ml, 2.37 mmol) was added, and the mixture was stirred for 1.5 hours under heating. After cooling, the reaction mixture was extracted with ethyl acetate, the organic layer was washed with an aqueous sodium chloride solution and dried with $MgSO_4$, and the solvent was distilled off under reduced pressure. Thus obtained residue was purified by silica gel chromatography, and after drying it was subjected to recrystallization with ethyl acetate-hexane to give a white crystalline plate (398 mg, 72%).

m.p. 113-115°C.

Elemental Analysis for $C_{25}H_{25}N_2O_4SF$:

	C(%)	H(%)	N(%)
Calcd.:	64.09 ;	5.38 ;	5.98
Found :	63.89 ;	5.39 ;	5.92.

^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.00(2H,quint,J=6.7Hz), 2.50(3H,s), 3.34(3H,s), 3.50(2H,t,J=6.7Hz), 3.83(3H,s), 4.18(2H,t,J=6.7Hz), 5.26(2H,s), 6.93(2H,d,J=8.8Hz), 7.07-7.12(2H,m), 7.24-7.29(4H,m).

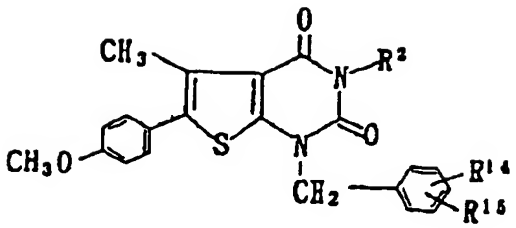
IR (KBr): 1700, 1659, 1473 cm^{-1}.

Reference Example 20

Employing the compounds which are produced in Reference Example 18 as a starting material, compounds which are produced in accordance with the method described in Reference Example 15 are set forth in

Table 6.

Table 6



Ref.Ex. 20 Cpd.No.	R^{14}, R^{15}	R^2	Yield (%)	m.p. (°C)
1	2,6-difluoro	methoxypropyl	76	173-174
2	2,6-difluoro	3-methyl-thiophenyl	39	243-245

Reference Example 21

Production of 2,4(1H,3H)-dioxo-3-phenyl-5-methyl-6-(4-methoxyphenyl)thieno[2,3-d]pyrimidine:

To a pyridine (30 ml) solution of the compound (5.00 g, 16.32 mmol) obtained in Reference Example 4, phenylisocyanate (2.66 ml, 24.48 mmol) was added. The mixture was stirred at 45°C for 6 hours, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethanol (6 ml). To the solution was added 28% sodium methoxide (7.86 g, 40.80 mmol), the mixture was stirred at room temperature for 2 hours, to the resultant was added 2N hydrochloric acid (25 ml, 50 mmol), and the solvent, ethanol, was distilled off under reduced pressure. Thus obtained residue was subjected to filtration, washed with water-ethanol, dried under reduced pressure, and recrystallized by ethanol to give yellow power (6.09 g, 98%).

m.p. >300°C.

Elemental Analysis for $C_{19}H_{13}N_3O_4S \cdot 0.3H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	59.30 ;	3.56 ;	10.92

Found : 59.56 ; 3.52 ; 10.93.

^{1}H-NMR (300MHz, DMSO-d_6) δ: 2.50(3H,s), 7.31-7.46(5H,m), 7.78(2H,d,J=8.8Hz), 8.32(2H,d,J=8.8Hz), 12.50(1H,s).

IR (KBr): 1715, 1657, 1593, 1510 cm^{-1}.

Reference Example 22

Production of 2,4(1H,3H)-dioxo-5-methyl-3-(3-methoxyphenyl)-6-(4-methoxyphenyl)thieno[2,3-d]pyrimidine:

In substantially the same procedure as described in Reference Example 21, using 3-methoxyphenylisocyanate (1.57 ml, 12.0 mmol) in place of phenylisocyanate, from the compound (3.06 g, 10.00 mmol) obtained in Reference Example 4 and 28% sodium methoxide (4.82 g, 25.00 mmol), the titled compound was produced as colorless crystals (3.15 g, 77%).

m.p. >300°C.

Elemental Analysis for $C_{20}H_{15}N_3O_5S$:

	C(%)	H(%)	N(%)
Calcd.:	58.67 ;	3.69 ;	10.26
Found :	58.76 ;	3.67 ;	10.32.

^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.50(3H,s), 3.78(3H,s), 6.87(1H,d,J=8.1Hz), 6.92(1H,s), 7.00(1H,d,J=8.1Hz), 7.38(1H,t,J=8.1Hz), 7.77(1H,d,J=8.7Hz), 8.31(2H,d,J=8.7Hz), 12.48(1H,s).

IR (KBr): 1717, 1661, 1593, 1510, 1429 cm^{-1}.

Reference Example 23

Production of 2,4(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-5-methyl-3-(3-methylsulfinylphenyl)-6-(4-methoxyphenyl)thieno[2,3-d]pyrimidine:

To a dichloromethane (20 ml) solution of the compound 2 (200 mg, 0.37 mmol) obtained in Reference Example 20 (Table 6), m-chloroperbenzoic acid (129 mg, 0.37 mmol) was added under ice-cooling. The mixture was stirred for 30 minutes, and the reaction mixture was subjected to distribution with dichloromethane and

an aqueous sodium chloride solution. The aqueous layer was extracted with dichloromethane, the combined extracts were dried with an aqueous sodium chloride solution and dried with $MgSO_4$, and the solvent was distilled off under reduced pressure. Thus obtained residue was purified by silica gel column chromatography to give white powders (183 mg, 89%).
m.p. 267-268°C.
^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.46(3H,s), 2.79(3H,s), 3.85(3H,s), 5.35(2H,s), 6.90-6.97(4H,m), 7.33-7.72(7H,m).
IR (KBr): 1717, 1667, 1628, 1562, 1533 cm^{-1}.
FAB-MS m/z: 553.1(MH^+).

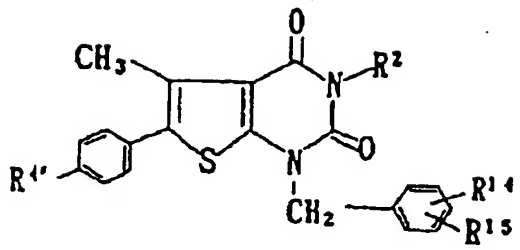
Reference Example 24

Production of 2,4(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-5-methyl-3-(3-methylsulfonylphenyl)-6-(4-methoxyphenyl)thieno[2,3-d]pyrimidine:

In substantially the same procedures as described in Reference Example 23, using m-chloroperbenzoic acid (62 mg, 0.18 mmol) again, from the compound (100 mg, 0.18 mmol) obtained in Reference Example 23, the titled compound was produced as colorless crystals (98 mg, 95%).
m.p. 256-257°C.
^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.46(3H,s), 3.10(3H,s), 3.85(3H,s), 5.36(2H,s), 6.90-6.97(4H,m), 7.29-8.01(7H,m).
IR (KBr): 1719, 1665, 1531, 1473 cm^{-1}.
FAB-MS m/z: 569.1(MH^+).

Reference Example 25

Employing the compounds which are produced in accordance with the methods of Reference Example 13, 14, 21 or 22 as a starting material, compounds which are produced in accordance with the method described in Reference Example 17 are set forth in Table 7.
Table 7



Ref.Ex.25 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	Yield (%)	m.p. (°C)
1	isobutyl	2-fluoro	methoxy	80	136-138
2	isobutyl	2,6-difluoro	methoxy	73	121-122
3	methoxyethyl	2-fluoro	methoxy	74	102-104
4	methoxyethyl	2,6-difluoro	methoxy	86	152-153
5	3,5-dimethoxyphenyl	2-fluoro	methoxy	76	250-252
6	3,5-dimethoxyphenyl	2,6-difluoro	methoxy	90	270-272
7	3,5-dimethoxyphenyl	2,6-difluoro	nitro	95	257-258
8	phenyl	2,6-difluoro	nitro	93	280-282
9	3-methoxyphenyl	2,6-difluoro	nitro	84	231-234
10	3-isopropoxy-phenyl	2,6-difluoro	nitro		
11	3-methoxy-methoxyphenyl	2,6-difluoro	nitro	88	209-210

Reference Example 26

Production of 2,4(1H,3H)-dioxo-1-(2-fluorobenzyl)-5-bromomethyl-6-(4-methoxyphenyl)-3-(3-methoxypropyl)thieno[2,3-d]pyrimidine:

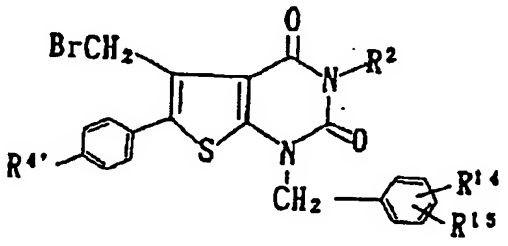
A mixture of the compound (270 mg, 0.576 mmol) obtained in Reference Example 19, N-bromosuccinimide (103 mg, 0.576 mmol), α,α'-azobisisobutylonitrile 10 mg, 0.058 mmol) and carbon tetrachloride (10 ml) was heated under reflux. After cooling, insolubles were removed by filtration, the filtrate was diluted with chloroform. The organic layer was washed with an aqueous sodium chloride solution and dried with $MgSO_4$, and then the solvent was distilled off under reduced

pressure. Thus obtained residue was recrystallized by ethyl acetate to give colorless powders (294 mg, 93%).
m.p. 105-107°C.
^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.01(2H,quint,J=6.7Hz), 3.33(3H,s), 3.50(2H,t,J=6.7Hz), 3.85(3H,s), 4.21(2H,t,J=6.7Hz), 4.81(2H,s), 5.27(2H,s), 6.98(2H,d,J=8.8Hz), 7.09-7.34(4H,m), 7.49(2H,d,J=8.8Hz).
IR (KBr): 1713, 1661, 1628, 1541 cm^{-1}.
FAB-MS m/z: 548.1(MH^+).

Reference Example 27

Employing the compounds which are produced in Reference Examples 19, 20, 23, 24 or 25 as starting materials, compounds which are produced in accordance with the method described in Reference Example 26 are set forth in Table 8.

Table 8



Ref.Ex.27 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	Yield (%)	m.p. (°C)
1	methoxypropyl	2,6-difluoro	methoxy	77	166-167
2	3-methyl-mercaptophenyl	2,6-difluoro	methoxy	90	228-230
3	3-methyl-sulfinylphenyl	2,6-difluoro	methoxy	85	272-273
4	3-methyl-sulfonylphenyl	2,6-difluoro	methoxy	100	261-263
5	isobutyl	2-fluoro	methoxy	79	125-127
6	isobutyl	2,6-difluoro	methoxy	88	155-157
7	methoxylethyl	2-fluoro	methoxy	87	152-153
8	methoxylethyl	2,6-difluoro	methoxy	88	150-151

Ref.Ex.27 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	Yield (%)	m.p. (°C)
9	3,5-dimethoxy-phenyl	2-fluoro	methoxy	76	234-238
10	3,5-dimethoxy-phenyl	2,6-difluoro	methoxy	86	251-253
11	3,5-dimethoxy-phenyl	2,6-difluoro	nitro	91	245-247
12	phenyl	2,6-difluoro	nitro	94	228-229
13	3-methoxyphenyl	2,6-difluoro	nitro	91	253-254
14	3-isopropoxy-phenyl	2,6-difluoro	nitro		
15	3-methoxy-methoxyphenyl	2,6-difluoro	nitro	97	207-209

Example 1

Production of 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-3-phenyl-1-(2-fluorobenzyl)-5-(N-benzyl-N-methylaminomethyl)thieno[2,3-d]pyrimidine hydrochloride:

To a solution of the compound 5 produced in Reference Example 11 (0.150 g, 0.310 mmol) in dimethylformamide (10 ml), with ice-cooling, were added ethyldiisopropylamine (0.08 ml, 0.460 mmol) and methylbenzylamine (0.05 ml, 0.370 mmol). After stirring for 2 hours at room temperature, the reaction mixture was concentrated. The residue was partitioned between ethyl acetate and a saturated aqueous solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate. The combined organic layer was dried ($MgSO_4$). The solvent was distilled off under reduced pressure, and the residue was chromatographed on silica gel to give a colourless oil (0.159 g, 97%). To the solution of this oil in ethyl acetate (4 ml) was added, with ice-cooling, an 1N solution of hydrogen chloride in ether (0.3 ml). After stirring for 10 minutes under ice-cooling, the reaction mixture was concentrated with reduced pressure. The residue was crystallized from ethyl acetate-ether to give a titled

hydrochloride (0.144 g) as white crystals.
m.p. 140-143°C
Elemental Analysis for $C_{35}H_{30}N_3O_3SF \cdot HCl \cdot H_2O$:

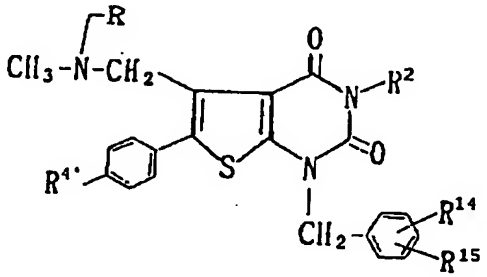
	C(%)	H(%)	N(%)
Calcd.:	65.05 ;	5.14 ;	6.50
Found :	65.14 ;	5.03 ;	6.37

IR(KBr) 1711, 1665, 1543, 1477 cm^{-1}.

Example 2

Starting from the compounds which are produced in Reference Example 11, compounds which are produced in accordance with the method described in Example 1 are set forth in Table 9.

Table 9



Ex.2 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	R	Yield (%)	m.p. (°C)
1	methyl	2-methoxy	methoxy	phenyl	46	119-122
2	methyl	2-fluoro	methoxy	phenyl	97	128-131
3	phenyl	2-methoxy	methoxy	phenyl	95	97-105
4	phenyl	2-fluoro	nitro	phenyl	100	140-143
5	phenyl	3-fluoro	methoxy	phenyl	97	152-156
6	phenyl	4-fluoro	methoxy	phenyl	100	165-170
7	phenyl	2,4-difluoro	methoxy	phenyl	77	155-160
8	phenyl	2,6-difluoro	methoxy	phenyl	100	160-162
9	phenyl	2-chloro, 6-fluoro	methoxy	phenyl	98	150-155

Ex.2 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	R	Yield (%)	m.p. (°C)
10	phenyl	2-methyl-thio	methoxy	phenyl	76	152-158
11	benzyl	2-fluoro	methoxy	phenyl	89	128-134
12	benzyl	2,6-difluoro	methoxy	phenyl	100	123-127
13	4-methoxy phenyl	2-fluoro	methoxy	phenyl	93	150-155
14	4-methoxy phenyl	2,6-difluoro	methoxy	phenyl	84	153-157
15	cyclohexyl	2-fluoro	methoxy	phenyl	93	144-150
16	cyclohexyl	2,6-difluoro	methoxy	phenyl	97	145-150
17	phenyl	2,6-difluoro	nitro	phenyl	93	155-160
18	2-methoxy-phenyl	2-fluoro	methoxy	phenyl	93	152-153
19	2-methoxy-phenyl	2,6-difluoro	methoxy	phenyl	100	148-150
20	3-methoxy-phenyl	2-fluoro	methoxy	phenyl	92	155-158
21	3-methoxy-phenyl	2,6-difluoro	methoxy	phenyl	91	160-163
22	2-chloro-phenyl	2-fluoro	methoxy	phenyl	97	147-152
23	2-chloro-phenyl	2,6-difluoro	methoxy	phenyl	98	150-155
24	3-chloro-phenyl	2-fluoro	methoxy	phenyl	100	148-153
25	3-chloro-phenyl	2,6-difluoro	methoxy	phenyl	100	152-157
26	4-chloro-phenyl	2-fluoro	methoxy	phenyl	91	161-164
27	4-chloro-phenyl	2,6-difluoro	methoxy	phenyl	86	145-146
28	3-methoxy-phenyl	2,6-difluoro	propyl-amino-carbonyl	phenyl		
29	3-methoxy-phenyl	2,6-difluoro	isopropyl-amino-carbonyl	phenyl		
30	3-isopropoxy-phenyl	2,6-difluoro	propyl-amino-carbonyl	phenyl		

Ex.2 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	R	Yield (%)	m.p. (°C)
31	3-isopropoxy-phenyl	2,6-difluoro	isopropyl-amino-carbonyl	phenyl		
32	3-methoxy-phenyl	2,6-difluoro	methoxy	phenyl	91	160-163
33	3-isopropoxy-phenyl	2,6-difluoro	methoxy	phenyl		
34	3-methoxy-phenyl	2,6-difluoro	methoxy	2-methylthio-phenyl		
35	3-methoxy-phenyl	2,6-difluoro	methoxy	2-pyridyl		
36	phenyl	2,6-difluoro	methoxy	2-methyl-thiophenyl		
37	phenyl	2,6-difluoro	methoxy	2-pyridyl		
38	phenyl	2,6-difluoro	methoxy	dimethyl-aminomethyl		
39	phenyl	2,6-difluoro	methoxy	diethyl-aminomethyl		
40	phenyl	2,6-difluoro	methoxy	1-pyrrolidi-nylmethyl		

Example 3

Production of 6-(4-aminophenyl)-2,4(1H,3H)-dioxo-1-(2-fluorobenzyl)-3-phenyl-5-(N-methyl-N-benzylaminomethyl)thieno[2,3-d]pyrimidine:

The compound 4 produced in Example 2 (0.15 g, 0.247 mmol) was dissolved in ethanol (15 ml), to which was added 10% palladium-carbon (15 mg). The mixture was hydrogenized for 8 hours at room temperature under atmospheric pressure in an atmosphere of hydrogen. The reaction mixture was filtrated with celite, and the filtrate was concentrated under reduced pressure. The concentrate was chromatographed on silica gel to give a yellow crystalline amorphous (0.046 g, 32%).

^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.05(3H,s), 3.57(2H,s), 3.81(2H,br s), 3.89(2H,s), 5.29(2H,s), 6.69(2H,d,J=8.7Hz), 7.05-7.56(16H,m).

FAB-Mass m/z 577$(MH)^+$

Example 4

Production of 6-(aminophenyl)-2,4-(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-5-(N-methyl-N-benzylaminomethyl)-3-phenylthieno[2,3-d]pyrimidine:

Starting from the compound No. 17 produced in Example 2, the titled compound as crystalline amorphous (65%) was produced in accordance with the method described in Example 3.

^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.05(3H,s), 3.56(2H,s), 3.81(2H,br s), 3.88(2H,s), 5.36(2H,s), 6.71(2H,d,J=8.7Hz), 6.91(2H,t,J=8.7Hz), 7.21-7.53(13H,m).

Example 5

Production of 6-(4-acetylaminophenyl)-2,4(1H,3H)-dioxo-1-(2-fluorobenzyl)-5-(N-methyl-N-benzylaminomethyl)-3-phenylthieno[2,3-d]pyrimidine:

The compound produced in Example 3 (0.63 g, 0.11 mmol) was dissolved in anhydrous pyridine (5 ml), to which was added acetic anhydride (0.01 ml, 0.11 mmol). The mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The concentrate was partitioned between methylene chloride (30 ml) and a saturated aqueous sodium chloride solution (10 ml). The aqueous layer was again extracted with methylene chloride (30 ml). The combined organic layer was dried over magnesium sulfate, which was concentrated under reduced pressure. The concentrate was chromatographed on silica gel to give a colorless solid (0.01 g, 15%).

^{1}H-NMR (300MHz, $CDCl_3$) δ: 2.06(3H,s), 2.19(3H,s), 3.57(2H,s), 3.90(2H,s), 5.30(2H,s), 7.04-7.57(16H,s), 7.70(2H,d,J=8.4Hz).

Example 6

Employing the compound produced in Example 3, as the starting material, in accordance with substantially

the same procedure as described in Example 5, the following compounds were produced.

No. 1: 2,4(2H,3H)-Dioxo-1-(2-fluorobenzyl)-5-(N-methyl-N-benzylaminomethyl)-3-phenyl-6-(4-propionylaminophenyl)thieno[2,3-d]pyrimidine hydrochloride (yield: 86%, m.p. 172-175°C)

No. 2: 2,4(2H,3H)-Dioxo-1-(2-fluorobenzyl)-6-(4-isobutyrylaminophenyl)-5-(N-methyl-N-benzylaminomethyl)-3-phenylthieno[2,3-d]pyrimidine hydrochloride (yield: 77%, m.p. 185-188°C)

No. 3: 2,4(2H,3H)-Dioxo-1-(2-fluorobenzyl)-6-(4-methoxyacetylaminophenyl)-5-(N-methyl-N-benzylaminomethyl)-3-phenylthieno[2,3-d]pyrimidine hydrochloride (yield: 88%, m.p. 157-162°C)

Example 7

Production of 2,4(1H,3H)-dioxo-1-(2-fluorobenzyl)-5-(N-benzyl-N-methylaminomethyl)-6-(4-methoxyphenyl)-3-(3-methoxypropyl)thieno[2,3-d]pyrimidine:

To a dimethylformamide (10 ml) solution of the compound (284 mg, 0.519 mmol) obtained in Reference Example 26 were added ethyldiisopropylamine (0.140 ml, 0.780 mmol) and methylbenzylamine (0.080 ml, 0.620 mmol). The mixture was stirred at room temperature for 2 hours, the reaction mixture was concentrated, and the obtained residue was subjected to distribution with ethyl acetate and saturated sodium bicarbonate. The aqueous layer was extracted with ethyl acetate. The extract and the organic layer were combined, dried with $MgSO_4$, and the solvent was distilled off under reduced pressure. Thus obtained residue was purified by silica gel column chromatography to give colorless oily substance (280 mg, 92%). The oily substance was dissolved in ethyl acetate (4 ml), and to the solution 1N solution of hydrogen chloride in ether (0.3 ml) under ice-cooling. The mixture was stirred under ice-cooling, and the reaction mixture was concentrated

under reduced pressure. The residue was subjected to crystallization with ethyl acetate-ether to give a hydrochloride of the titled compound (220 mg) was obtained as white crystals.

m.p. 95-100°C.

Elemental Analysis for $C_{35}H_{34}N_3O_4SF \cdot 1.0HCl \cdot 0.5H_2O$:

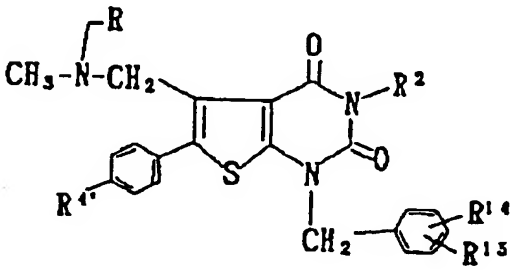
	C(%)	H(%)	N(%)
Calcd.:	62.60 ;	5.73 ;	6.64
Found :	62.73 ;	5.67 ;	6.56.

IR (KBr): 1702, 1657, 1562, 1543, 1489 cm^{-1}.

Example 8

Starting from the compounds which are produced in Reference Example 27, compounds which are produced in accordance with the method described in Example 7 are set forth in Table 10. The compound 19 and 20 are produced by hydrolyzing the compound 21 to produce the compound 22, and by reacting the compound 22 with alkyl halide in the presence of a base.

Table 10



Ex.8 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	R	Yield (%)	m.p. (°C)
1	methoxypropyl	2,6-difluoro	methoxy	phenyl	69	95-100
2	3-methyl-thiophenyl	2,6-difluoro	methoxy	phenyl	94	139-144
3	3-methyl-sulfinylphenyl	2,6-difluoro	methoxy	phenyl	93	153-156
4	3-methyl-sulfonylphenyl	2,6-difluoro	methoxy	phenyl	98	155-159

Ex.8 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	R	Yield (%)	m.p. (°C)
5	isobutyl	2-fluoro	methoxy	phenyl	100	150-153
6	isobutyl	2,6-difluoro	methoxy	phenyl	98	165-167
7	methoxyethyl	2-fluoro	methoxy	phenyl	95	154-156
8	methoxyethyl	2,6-difluoro	methoxy	phenyl	91	126-130
9	3,5-dimethoxy-phenyl	2-fluoro	methoxy	phenyl	90	140-145
10	3,5-dimethoxy-phenyl	2,6-difluoro	mthoxy	phenyl	91	146-148
11	3,5-dimethoxy-phenyl	2,6-difluoro	nitro	phenyl	97	142-146
12	phenyl	2,6-difluoro	nitro	phenyl	93	152-153
13	3-methoxy-phenyl	2,6-difluoro	nitro	phenyl	82	142-144
14	3-isopropoxy-phenyl	2,6-difluoro	nitro	phenyl	70	amorphous (80-90)
15	3-isopropoxy-phenyl	2,6-difluoro	nitro	2-thiomethyl-phenyl		
16	3-isopropoxy-phenyl	2,6-difluoro	nitro	2-pyridyl		
17	3-methoxy-phenyl	2,6-difluoro	nitro	2-thiomethyl-phenyl		
18	3-methoxy-phenyl	2,6-difluoro	nitro	2-pyridyl		
19	3-ethoxyphenyl	2,6-difluoro	nitro	phenyl	93	171-176
20	3-propoxy-phenyl	2,6-difluoro	nitro	phenyl	86	149-151
21	3-methoxy-methoxyphenyl	2,6-difluoro	nitro	phenyl	86	110-120
22	3-hydroxy-phenyl	2,6-difluoro	nitro	phenyl	86	207-209
23	3-methoxy-phenyl	2,6-difluoro	nitro	diethyl-aminomethyl		
24	3-methoxy-phenyl	2,6-difluoro	nitro	dimethyl-aminomethyl		

Ex.8 Cpd.No.	R^2	R^{14}, R^{15}	$R^{4'}$	R	Yield (%)	m.p. (°C)
25	3-methoxy-phenyl	2,6-difluoro	nitro	1-pyrroli-dinylmethyl		

Example 9

Production of 6-(4-aminophenyl)-2,4(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-5-(N-benzyl-N-methylaminomethyl)-3-(3-methoxyphenyl)thieno[2,3-d]pyrimidine hydrochloride:

To a formic acid (200 ml) solution of the compound 13 produced in Example 8, 50% paradium-carbon powder (0.90 g) was added under ice-cooling, and the mixture was stirred for 2 hours in a hydrogen atmosphere at room temperature. The reaction mixture was concentrated, and the residue was subjected to distribution with dichloromethan and saturated sodium bicarbonate. The aqueous layer was extracted with dichloromethane, and the extract was combined with the organic layer. The mixture was dried with $MgSO_4$, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to give colorless powders (5.13 g, 60%). Thus obtained compound (100 mg) was dissolved in ethyl acetate (4 ml), and to the solution was added 1N solution of hydrogen chloride in ether (0.3 ml) under ice-cooling and the mixture was stirred for 10 minutes under ice-cooling. The reaction mixture was concentrated under reduced pressure, and the residue was crystallized from ethyl acetate-ether to give hydrochloride of the titled compound (95 mg) was obtained as white crystals.

m.p. 162-165°C.

Elemental Analysis for $C_{35}H_{30}N_4O_3SF_2 \cdot 2.0HCl \cdot 1.0H_2O$:

C(%) H(%) N(%)

Calcd.: 58.74 ; 4.79 ; 7.83

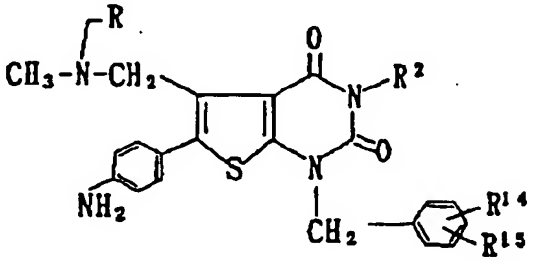
Found : 58.44 ; 4.72 ; 7.66.

IR (KBr): 1715, 1659, 1537, 1473 cm^{-1}.

Example 10

Starting from the compounds which are produced in Example 8, compounds which are produced in accordance with the method described in Example 9 are set forth in Table 11.

Table 11



Ex.10 Cpd.No.	R^2	R^{14}, R^{15}	R	Yield (%)	m.p. (°C)
1	3,5-dimethoxy-phenyl	2,6-difluoro	phenyl	69	95-100
2	phenyl	2,6-difluoro	phenyl	94	139-144
3	3-isopropoxy-phenyl	2,6-difluoro	phenyl	77	138-140
4	3-isopropoxy-phenyl	2,6-difluoro	2-methylthio-phenyl		
5	3-isopropoxy-phenyl	2,6-difluoro	2-pyridyl		
6	3-methoxyphenyl	2,6-difluoro	2-methylthio-phenyl		
7	3-methoxyphenyl	2,6-difluoro	2-pyridyl		
8	3-ethoxyphenyl	2,6-difluoro	phenyl	67	169-172
9	3-propoxyphenyl	2,6-difluoro	phenyl	73	115-120
10	3-methoxyphenyl	2,6-difluoro	diethylamino-methyl		
11	3-methoxyphenyl	2,6-difluoro	dimethylamino-methyl		

Ex.10 Cpd.No.	R^2	R^{14}, R^{15}	R	Yield (%)	m.p. (°C)
12	3-methoxyphenyl	2,6-difluoro	1-pyrrolidinylmethyl		

Example 11

Production of 2,4(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-5-(N-benzyl-N-methylaminomethyl)-6-(4-formamidophenyl)-3-phenylthieno[2,3-d]pyrimidine:

Formic acid (0.5 ml, 13.3 mmol) was added to acetic anhydride (1.0 ml, 10.6 mmol) under ice-cooling, the mixture was stirred for one hour at 50°C to give formic acid-acetic acid anhydride. To a tetrahydrofuran (10 ml) solution of the compound 2 (200 mg, 0.34 mmol) obtained in Example 10 was added the formic acid-acetic acid anhydride (0.3 ml) under ice-cooling and the mixture was stirred for 30 minutes. The mixture was stirred for one hour. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give colorless solid substance (125 mg) of the titled compound.

m.p. 194-196°C.

Elemental Analysis for $C_{35}H_{30}N_4O_3SF_2 \cdot 0.5H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	66.55 ;	4.63 ;	8.87
Found :	66.74 ;	4.56 ;	8.88.

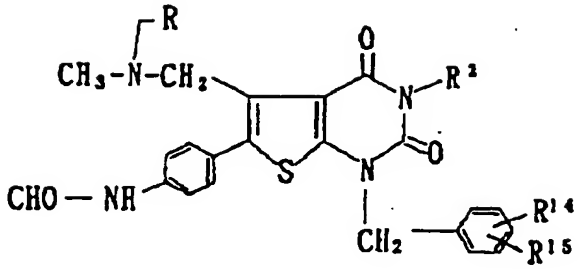
^{1}H-NMR (300MHz, $CDCl_3$) δ: 3.57(2H,s), 3.90(2H,s), 5.37(2H,s), 6.90-7.30(12H,m), 7.34-7.79(6H,m), 8.42(1H,s).

IR (KBr): 1715, 1665, 1531, 1467 cm^{-1}.

Example 12

Starting from the compounds which are produced in Example 9 or 10, compounds which are produced in accordance with the method described in Example 11 are set forth in Table 12.

Table 12



Ex.12 Cpd.No.	R^2	R^{14}, R^{15}	R	Yield (%)	m.p. (°C)
1	3,5-dimethoxy-phenyl	2,6-difluoro	phenyl	55	239-243
2	3-methoxyphenyl	2,6-difluoro	phenyl	56	213-215
3	3-isopropoxy-phenyl	2,6-difluoro	phenyl		
4	3-isopropoxy-phenyl	2,6-difluoro	2-methylthio-phenyl		
5	3-isopropoxy-phenyl	2,6-difluoro	2-pyridyl		
6	3-methoxyphenyl	2,6-difluoro	2-methylthio-phenyl		
7	3-methoxyphenyl	2,6-difluoro	2-pyridyl		

Example 13

Production of 2,4(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-5-(N-benzyl-N-methylaminomethyl)-6-(4-methylaminophenyl)-3-(3-methoxyphenyl)thieno[2,3-d]pyrimidine hydrochloride:

To a tetrahydrofuran (30 ml) solution of the compound 2 (730 mg, 1.12 mmol) obtained in Example 12 was added dimethylsulfid borane (0.28 ml, 2.8 mmol) under ice-cooling, and the mixture was heated for 2 hours under reflux. After adding hydrochloric acid (pH<2) and then heating under reflux for 1 hour, the resultant was concentrated and the residue was subjected to distribution with dichloromethane and saturated sodium bicarbonate. The aqueous layer was extracted with dichloromethane, the extract was combined with organic layer, the mixture was dried with

$MgSO_4$ and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to give colorless powder (610 mg, 85%). To the ethyl acetate (4 ml) solution of thus obtained compound was added 1N solution of hydrogen chloride in ether (0.3 ml under ice-cooling, and the mixture was stirred for 10 minutes under ice-cooling. The residue obtained by concentrating the reaction mixture under reduced pressure was subjected to crystallization to give white crystals (95 mg) of hydrochloride of the titled compound.

m.p. 155-160°C.

Elemental Analysis for

$C_{35}H_{30}N_4O_3SF_2 \cdot 2.0HCl \cdot 0.5AcOEt \cdot 3.0H_2O$:

	C(%)	H(%)	N(%)
Calcd.:	56.36 ;	5.47 ;	6.91
Found :	56.08 ;	5.22 ;	6.86.

IR (KBr): 1715, 1663, 1607, 1543, 1475 cm^{-1}.

Example 14

Production of 2,4(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-6-(4-propionylaminophenyl)-5-(N-benzyl-N-methylaminomethyl)-3-(3-methoxyphenyl)thieno[2,3-d]pyrimidine hydrochloride:

To a dichloromethane (10 ml) solution of the compound (250 mg, 0.38 mmol) obtained in Example 9 were added triethylamine (0.053 mg, 0.38 mmol) and propionyl chloride (0.033 ml, 0.38 mmol) under ice-cooling, and the mixture was stirred one hour. The reaction mixture was subjected to distribution with dichloromethane and saturated sodium bicarbonate. The aqueous layer was extracted with dichloromethane, the extracts were combined, the combined extracts were washed with an aqueous solution of sodium chloride and dried with $MgSO_4$, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography to give colorless oily substance

(220 mg, 82%). To an ethyl acetate (4 ml) solution of thus obtained acyl derivative was added 1N solution of hydrogen chloride in ether (0.3 ml) under ice-cooling and the mixture was stirred for 10 minutes under ice-cooling. The reaction mixture was concentrated under reduced pressure, the residue was crystallized to give white crystals of hydrochloride (213 mg) of the titled compound.

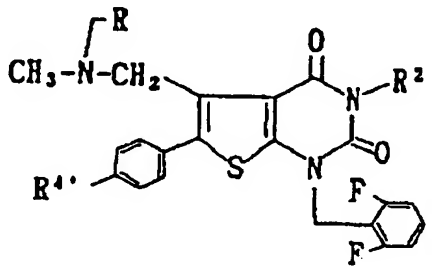
m.p. 218-224°C.

IR (KBr): 1713, 1665, 1601, 1543, 1475 cm^{-1}.

Example 15

Starting from the compounds which are produced in Example 9 or 10, compounds which are produced in accordancd with the method described in Example 14 are set forth in Table 13.

Table 13



Ex.15 Cpd.No.	R^2	$R^{4'}$	R	Yield (%)	m.p. (°C)
1	3-methoxyphenyl	isobutyryl-amino	phenyl	85	170-173
2	phenyl	isobutyryl-amino	phenyl	67	185-190
3	3,5-dimethoxy-phenyl	propionyl-amino	phenyl	82	218-224
4	3,5-dimethoxy-phenyl	isobutynyl-amino	phenyl	76	240-245
5	3-methoxyphenyl	N-methyl-N-propionyl-amino	phenyl	84	138-143
6	3-methoxyphenyl	N-methyl-N-isobutyryl-amino	phenyl	91	146-152
7	phenyl	propionyl-amino	phenyl	78	197-202

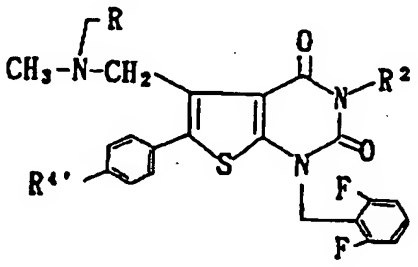
Ex.15 Cpd.No.	R^2	$R^{4'}$	R	Yield (%)	m.p. (°C)
8	phenyl	butyryl-amino	phenyl	76	169-170
9	phenyl	benzoyl-amino	phenyl	81	167-169
10	3-methoxyphenyl	propionyl-amino	phenyl	83	170-175
11	3-isopropoxy-phenyl	isobutyryl-amino	phenyl		
12	3-isopropoxy-phenyl	isobutyryl-amino	2-methylthio-phenyl		
13	3-isopropoxy-phenyl	isobutyryl-amino	2-pyridyl		
14	3-methoxyphenyl	isobutyryl-amino	3-methylthio-phenyl		
15	3-methoxyphenyl	isobutyryl-amino	2-pyridyl		
16	3-isopropoxy-phenyl	propionyl-amino	phenyl	94	179-181
17	3-ethoxyphenyl	propionyl-amino	phenyl	67	164-168
18	3-propoxyphenyl	propionyl-amino	phenyl	87	165-170
19	3-methoxyphenyl	ethylsul-fonylamino	phenyl		
20	3-methoxyphenyl	trifluoro-acetylamino	phenyl		
21	3-methoxyphenyl	isobutyryl-amino	diethylamino-methyl		
22	3-methoxyphenyl	isobutyryl-amino	dimethylamino-methyl		
23	3-methoxyphenyl	isobutyryl-amino	1-pyrrolidinyl-methyl		

Example 16

In substantially the same procedure as described in Example 14, using the compound which are obtained in Example 9 or 10 and anhydrous trifluoro acetic acid in place of propionyl chloride, trifluoroacetylamino derivative are obtained. To the derivative is added halogeno derivative (e.g. propyl bromide, isopropyl bromide) in the presence of an appropriate base (e.g. potassium carbonate) in a solvent (e.g.

dimethylformamide) which does not affect the reaction, the mixture is stirred for 1 to 6 hours at room temperature. To the reaction mixture is added 2N aqueous sodium hydroxide solution for hydrolysis for 1 to 2 hours to give compounds set forth in Table 14.

Table 14



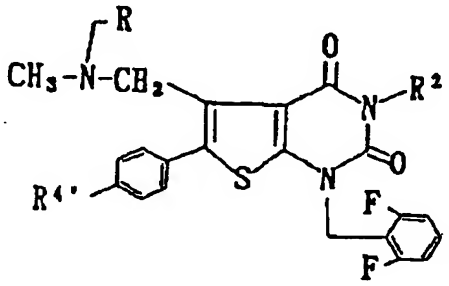
Ex. 16 Cpd.No.	R^2	$R^{4'}$	R
1	3-methoxyphenyl	propylamino	phenyl
2	3-methoxyphenyl	isopropylamino	phenyl
3	3-isopropoxy-phenyl	propylamino	phenyl
4	3-isopropoxy-phenyl	isopropylamino	phenyl
5	3-isopropoxy-phenyl	propylamino	2-methylthio-phenyl
6	3-isopropoxy-phenyl	propylamino	2-pyridyl
7	3-isopropoxy-phenyl	isopropylamino	2-methylthio-phenyl
8	3-isopropoxy-phenyl	isopropylamino	2-pyridyl
9	3-methoxyphenyl	ethylamino	phenyl
10	3-isopropoxy-phenyl	ethylamino	phenyl
11	3-methoxyphenyl	isopropylamino	2-methylthio-phenyl
12	3-methoxyphenyl	isopropylamino	2-pyridyl
13	3-methoxyphenyl	propylamino	2-methylthio-phenyl
14	3-methoxyphenyl	propylamino	2-pyridyl

Ex. 16 Cpd.No.	R^2	$R^{4'}$	R
15	3-methoxyphenyl	propylamino	diethylamino-methyl

Example 17

Employing the compounds which are obtained in Example 9 or 10 as starting compounds, the compounds set forth in Table 15 are produced by reacting the starting compounds with isoamyl nitrite, vinyl compound and palladium compound (e.g. tetrakistriphenylphosphine palladium, dibenzylideneacetone palladium) in acetic acid under stirring at a room temperature or under heating for 1 to 6 hours.

Table 15



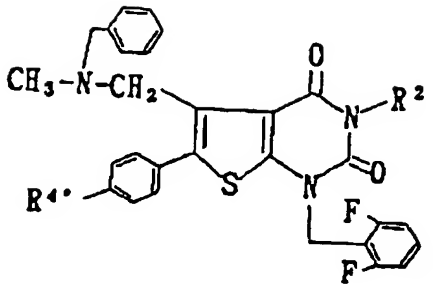
Ex. 17 Cpd.No.	R^2	$R^{4'}$	R
1	3-methoxyphenyl	ethoxycarbonyl-vinyl	phenyl
2	3-methoxyphenyl	ethoxycarbonyl-vinyl	2-methylthio-phenyl
3	3-methoxyphenyl	ethoxycarbonyl-vinyl	2-pyridyl
4	3-methoxyphenyl	propionylvinyl	phenyl
5	3-methoxyphenyl	propionylvinyl	2-methylthio-phenyl
6	3-methoxyphenyl	propionylvinyl	2-pyridyl
7	3-isopropoxy-phenyl	ethoxycarbonyl-vinyl	phenyl

Ex. 17 Cpd.No.	R^2	$R^{4'}$	R
8	3-isopropoxy-phenyl	propionylvinyl	phenyl
9	3-isopropoxy-phenyl	ethoxycarbonyl-vinyl	2-methylthio-phenyl
10	3-isopropoxy-phenyl	ethoxycarbonyl-vinyl	2-pyridyl
11	3-isopropoxy-phenyl	propionylvinyl	2-methylthio-phenyl
12	3-isopropoxy-phenyl	propionylvinyl	2-pyridyl
13	3-methoxyphenyl	propionylvinyl	dimethyl-aminomethyl
14	3-methoxyphenyl	propionylvinyl	1-pyrrolidinyl-methyl
15	3-methoxyphenyl	propionylvinyl	diethylamino-methyl

Example 18

To a mixture of the compound 30 or 31 which are obtained in Reference Example 9, a small amount of arylborric acid derivative, 2M aqueous sodium carbonate solution and 1,2-dimethoxyethane, is added a catalytic amount of tetrakis(triphenylphosphine)palladium(0), and thus obtained mixture is stirred under reflux for 2 hours. To the resulting compound, N-methylbenzylamino group is introduced in accordance with the method described in Reference Example 26 and Example 1 to give compounds set forth in Table 16.

Table 16

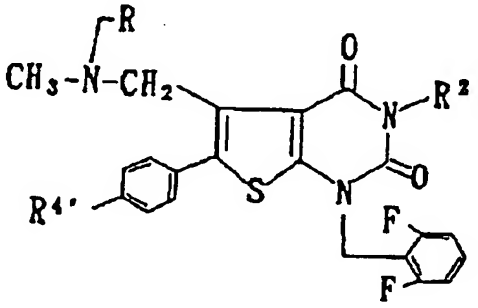


Ex. 18 Cpd.No.	R^2	$R^{4'}$
1	3-methoxyphenyl	propylaminocarbonyl
2	3-isopropoxyphenyl	propylaminocarbonyl
3	3-methoxyphenyl	isopropylaminocarbonyl
4	3-isopropoxyphenyl	isopropylaminocarbonyl
5	3-methoxyphenyl	ethylaminocarbonyl
6	3-methoxyphenyl	N-methyl-N-propyl-aminocarbonyl

Example 19

To the compounds which are obtained in Example 2, 3 equivalents of dimethylsulfide and 3 equivalents of aluminium chloride are added in dichloromethane under ice-cooling. The mixture is stirred for 1 to 4 hours to give R^4 phenol derivative. Thus obtained compound, a small amount of an alkyl halide (e.g. chloro acetone) and a base (e.g. potassium carbonate) are mixed in dimethylformamide to produce compounds set forth in Table 17.

Table 17



Ex. 19 Cpd.No.	R^2	$R^{4'}$	R
1	phenyl	acetonyloxy	phenyl
2	phenyl	acetonyloxy	2-methylthio-phenyl
3	phenyl	acetonyloxy	2-pyridyl
4	phenyl	acetonyloxy	diethylamino-methyl
5	phenyl	acetonyloxy	dimethylamino-methyl
6	phenyl	acetonyloxy	1-pyrrolidinyl-methyl
7	phenyl	allyloxy	phenyl
8	phenyl	propoxy	phenyl
9	phenyl	isobutoxy	phenyl
10	phenyl	cyclopropyl methoxy	phenyl
11	phenyl	allyloxy	diethylamino-methyl
12	phenyl	propoxy	diethylamino-methyl

Example 20

Using the compound produced in Example 4 (100 mg), lactose (165 mg), corn starch (5 mg), polyvinyl alcohol (4 mg) and magnesium stearate (1 mg), a tablet is prepared by a conventional method.

Example 21

The compound produced in Example 4 (5 g) is dissolved in distilled water for injection to make the whole volume 100 ml. The solution is subjected to sterilized filtration with 0.22 μm membrane filter (manufactured by Sumitomo Electric Industries, Ltd. or by Zartolius, Inc.), 2 ml each of which is distributed to sterilized vials, followed by lyophilization by a conventional means to give lyophilized injectable solution of 100 mg/vial.

Example 22

Using the compound 1 produced in Example 15 (100 mg), lactose (165 mg), corn starch (25 mg), polyvinyl alcohol (4 mg) and magnesium stearate (1 mg), a tablet is prepared by a conventional method.

Example 23

The compound 1 produced in Example 15 (5 g) is dissolved in distilled water for injection to make the whole volume 100 ml. This solution is subjected to sterilized filtration with 0.22 μm membrane filter (manufactured by Sumitomo Electric Industries, Ltd. or Zartolius, Inc.), 2 ml each of which is distributed to sterilized vials, followed by lyophilization by a conventional means to prepare lyophilized injectable solution of 100 mg/vial.

Example 24

(1)	Compound produced in Example 4 or the compound 1 of Example 15	5 g
(2)	Lactose.crystalline cellulose (granules)	330 g
(3)	D-mannitol	29 g
(4)	Low-substituted hydroxypropyl cellulose	20 g
(5)	Talc	25 g
(6)	Hydroxypropyl cellulose	50 g
(7)	Aspartame	3 g
(8)	Dipotassium glycyrrhetinate	3 g
(9)	Hydroxypropylmethyl cellulose 2910	30 g
(10)	Titanium oxide	3.5 g
(11)	Yellow iron sesquioxide	0.5 g
(12)	Light silicic acid anhydride	1 g

In refined water are suspended or dissolved (1), (3), (4), (5), (7) and (8). The nuclear granule of (2) is coated with the suspension or solution to prepare raw fine granules, which are coated with (9)-(11) to prepare coated fine granules, which are mixed with (12), to give 500 g of fine granules containing 1% of

the compound produced in Example 4 or the compound 1 of Example 15. 500 mg each of thus-prepared fine granules is packed.

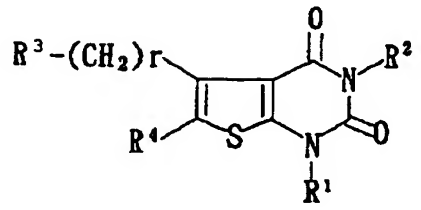
Industrial Applicability

A thienopyrimidine derivative (I) of the present invention is effective as a propylactic or therapeutic agent for the prevention or treatment of several hormone dependent diseases, for example, a sex hormone dependent cancer (e.g. prostatic cancer, cancer of uterine cervix, breast cancer, pituitary adenoma), benign prostatic hypertrophy, myoma of the uterus, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, polycystic ovary syndrome and acne vulgaris; is effective as a fertility controlling agent in both sexes (e.g. a pregnancy controlling agent and a menstrual cycle controlling agent); can be used as a contraceptive of male or female, as an ovulation-inducing agent of female; can be used as an infertility treating agent by using a rebound effect owing to a stoppage of administration thereof; is useful as modulating estrous cycles in animals in the field of animal husbandry, as an agent for improving the quality of edible meat or promoting the growth of animals; and is useful as an agent of spawning promotion in fish.

CLAIMS

What we claim is:

1. A compound of the formula:



(I)

wherein R^1 is hydrogen, an alkyl group or a group of the formula:

$$Q-(CH_2)p-$$

in which Q is (1) an aryl group which may be substituted by one or more of (i) halogen, (ii) nitro, (iii) cyano, (iv) amino, (v) an optionally substituted carboxyl, (vi) alkylenedioxy and (vii) a group of the formula: $-A-R^5$ in which A is a chemical bond or a spacer group and R^5 is an alkyl group, (2) an optionally substituted cycloalkyl group or (3) an optionally substituted heterocyclic group, and p is an integer of 0 to 3;

R^2 is hydrogen, an alkyl group which may be substituted by alkoxy, an optionally substituted aryl group, an optionally substituted aralkyl group or an optionally substituted cycloalkyl group;

R^3 is an optionally substituted amino group; r is an integer of 0 to 3; and

R^4 is an optionally substituted aryl group;

or a salt thereof.

2. A compound according to claim 1, wherein the spacer group represented by A is -O- or -S(O)m- in which m is an integer of 0 to 2.

3. A compound according to claim 1, wherein R^1 is a group of the formula:

$Q-(CH_2)p-$

in which Q is an aryl group which may be substituted by one or more of (i) halogen and (ii) a group of the formula: $-A-R^5$ in which A is -O- or -S(O)m- wherein m is an integer of 0 to 2 and R^5 is an alkyl group; and p is an integer of 0 to 3.

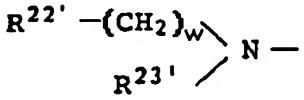
4. A compound according to claim 1, wherein R^2 is (1) an alkyl group which may be substituted by alkoxy, (2) an aryl group which may be substituted by one or more of (i) amino, (ii) acyl, (iii) carbamoyl, (iv) carboxy, (v) nitro, (vi) hydroxy, (vii) alkoxy group which may be substituted by alkoxy, (viii) halogen and (ix) a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is an alkyl group, (3) an aralkyl group which may be substituted by halogen or (4) cycloalkyl group.

5. A compound according to claim 4, wherein R^2 is (1) an alkyl group which may be substituted by alkoxy, (2) an aryl group which may be substituted by one or more of (i) hydroxy, (ii) an alkoxy group which may be substituted by alkoxy, (iii) halogen and (iv) a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is an alkyl group, (3) an aralkyl group or (4) a cycloalkyl group.

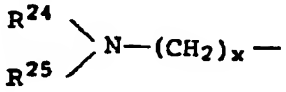
6. A compound according to claim 4, wherein R^2 is an aryl group which may be substituted by one or more of (1) an alkoxy group which may be substituted by alkoxy, (2) halogen and (3) a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is an alkyl group.

7. A compound according to claim 1, wherein R^3 is an

optionally substituted amino group of the formula:

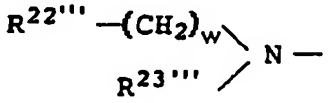


wherein $R^{22'}$ is (1) an aryl group which may be substituted by one or more of (i) amino, (ii) acyl, (iii) carbamoyl, (iv) carboxy, (v) nitro, (vi) hydroxy, (vii) alkoxy group which may be substituted by alkoxy, (viii) halogen, (ix) alkyl and (x) a group of the formula: -S(O)n-R^6 in which n is an integer of 0 to 2 and R^6 is an alkyl group, (2) a heterocyclic group which may be substituted by one or more of (i) amino, (ii) acyl, (iii) carbamoyl, (iv) carboxy, (v) nitro, (vi) hydroxy, (vii) alkoxy, (viii) halogen, (ix) alkyl and (x) a group of the formula: -S(O)n-R^6 in which n is an integer of 0 to 2 and R^6 is alkyl group, (3) an aralkyl group which may be substituted by halogen, (4) a group of the formula:



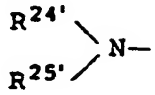
wherein R^{24} is hydrogen, an alkyl group or an aryl group, R^{25} is hydrogen or an alkyl group and R^{24} and R^{25} may form a 5 to 7 membered cyclic amino group containing the adjacent nitrogen atom which may be substituted and x is an integer of 0 to 3 or (5) an alkyl group which may be substituted by alkylthio, w is an integer of 0 to 3; and $R^{23'}$ is hydrogen or an alkyl group.

8. A compound according to claim 1, wherein R^3 is an optionally substituted amino group of the formula:



wherein $R^{22'''}$ is (1) an aryl group which may be substituted by alkylthio, (2) a heterocyclic group, (3)

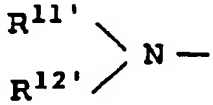
a group of the formula:



wherein $R^{24'}$ is hydrogen or alkyl, $R^{25'}$ is hydrogen or alkyl, and $R^{24'}$ and $R^{25'}$ may form a 5 to 7 membered cyclic amino group containing the adjacent nitrogen atom or (4) an alkyl group which may be substituted by alkylthio, w is an integer of 0 to 3; and $R^{23'''}$ is hydrogen or an alkyl group.

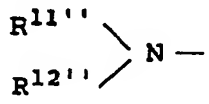
9. A compound according to claim 1, wherein R^4 is an aryl group which may be substituted by one or more of (1) an optionally substituted amino group, (2) acyl, (3) an optionally substituted carbamoyl group, (4) carboxy, (5) nitro, (6) hydroxy, (7) an optionally substituted alkoxy group and (8) an optionally substituted alkenyl group.

10. A compound according to claim 1, wherein R^4 is an aryl group which may be substituted by one or more of (1) a group of the formula:



wherein $R^{11'}$ is (i) hydrogen, (ii) alkyl, (iii) an optionally substituted alkoxy group, (iv) an optionally substituted acyl or (v) a group of the formula: -S(O)n-R^6 in which n is an integer of 0 to 2 and R^6 is an alkyl group and $R^{12'}$ is hydrogen or alkyl, (2) acyl, (3) carbamoyl, (4) N-mono or di-alkylcarbamoyl, (5) nitro, (6) alkoxy which may be further substituted by one or more of alkoxy, alkanoyl, oxo, hydroxy, cycloalkyl and halogen, (7) alkenyl which may be further substituted by alkoxycarbonyl or an alkylcarbonyl and (8) alkenyloxy.

11. A compound according to claim 1, wherein R^4 is aryl group which may be substituted by one or more of (1) a group of the formula:



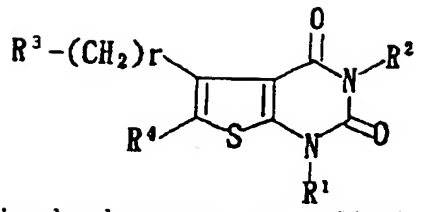
wherein $R^{11''}$ is (i) hydrogen, (ii) alkyl, (iii) alkoxy which may be substituted by halogen or alkoxy, (iv) formyl, (v) alkanoyl which may be substituted by halogen or alkoxy, (vi) benzoyl or (vii) a group of the formula: $-S(O)n-R^6$ in which n is an integer of 0 to 2 and R^6 is alkyl group and $R^{12''}$ is hydrogen or alkyl, (2) alkoxy which may be substituted by alkoxy, alkanoyl or cycloalkyl, (3) N-mono or di-alkylcarbamoyl, (4) nitro, (5) alkenyl which may be substituted by alkoxycarbonyl or alkylcarbonyl or (6) alkenyloxy.

12. A compound according to claim 1, which is 2,4(1H,3H)-dioxo-6-(4-methoxyphenyl)-3-phenyl-1-(2-chloro-6-fluorobenzyl)-5-(N-benzyl-N-methylaminomethyl)thieno[2,3-d]pyrimidine or its salt.

13. A compound according to claim 1, which is 2,4(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-6-(4-propionylaminophenyl)-5-(N-benzyl-N-methylaminomethyl)-3-(3-methoxyphenyl)thieno[2,3-d]pyrimidine or its salt.

14. A compound according to claim 1, which is 2,4(1H,3H)-dioxo-1-(2,6-difluorobenzyl)-6-(4-isobutyrylaminophenyl)-5-(N-benzyl-N-methylaminomethyl)-3-(3-methoxyphenyl)thieno[2,3-d]pyrimidine or its salt.

15. A method for producing a compound of the formula (I)



(I)

wherein R^1 is hydrogen, an alkyl or a group of the formula:

$$Q\text{-}(CH_2)p\text{-}$$

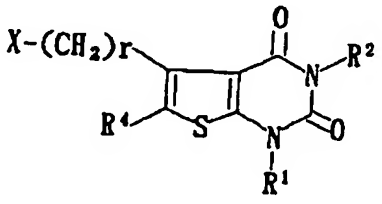
in which Q is (1) an aryl group which may be substituted by one or more of (i) halogen, (ii) nitro, (iii) cyano, (iv) amino, (v) an optionally substituted carboxyl, (vi) alkylenedioxy and (vii) a group of the formula: $-A-R^5$ in which A is a chemical bond or a spacer group and R^5 is an alkyl group, (2) an optionally substituted cycloalkyl group or (3) an optionally substituted heterocyclic group, and p is an integer of 0 to 3:

R^2 is hydrogen, an alkyl group which may be substituted by alkoxy, an optionally substituted aryl group, an optionally substituted aralkyl group or an optionally substituted cycloalkyl group;

R^3 is an optionally substituted amino group; r is an integer of 0 to 3; and

R^4 is an optionally substituted aryl group; or a salt thereof,

which comprises reacting a compound of the formula:



(II)

wherein R^1, R^2, R^4 and r have the same meaning as defined above, X is a leaving group, or a salt thereof with a compound of the formula:

$$R^3\text{-}H$$

wherein R^3 has the same meaning as defined above, or a

salt thereof.

16. A pharmaceutical composition, which comprises a compound as defined in claim 1 and a carrier, excipient or diluent therefor.

17. A composition according to claim 16, which is a gonadotropin-releasing hormone antagonistic composition.

18. A composition according to claim 16, which is a composition for preventing or treating a sex hormone dependent disease.

19. A method for antagonizing gonadotropin-releasing hormone in a mammal, which comprises administering an effective amount of a compound as defined in claim 1 to a mammal suffering from a gonadotropin-releasing hormone derived disorder.

20. A method according to claim 19, wherein the gonadotropin-releasing hormone derived disorder is a sex hormone dependent disease.

21. A compound as defined in claim 1 for medicinal use.

22. Use of a compound as defined in claim 1 for producing a gonadotropin-releasing hormone antagonistic composition for antagonizing gonadotropin-releasing hormone in a mammal suffering from a gonadotropin-releasing hormone derived disorder.

23. Use according to claim 22, wherein the gonadotropin-releasing hormone derived disorder is a sex hormone dependent disease.